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# The Effect of General Systemic Arteriosclerosis Upon the Heart and the Systemic Circulation*†

By George Fahr and Jay Davis, *Minneapolis, Minn.*

IT cannot be said that all of the factors possibly associated with the development of chronic nonvalvular heart disease have been adequately investigated. We have very good evidence that long continued high blood pressure will lead to failure of the left ventricle. We also know that arteriosclerosis of the coronary arteries leads to thrombosis and infarction of the heart with sudden death or acute onset of heart failure. Coronary sclerosis also very frequently leads to chronic heart failure through inadequate blood supply to the heart muscle. In as far as we are aware, the effect of generalized arteriosclerosis upon the work of the heart, upon the flow of blood through the systemic and coronary circulations, and upon the size of the heart has not been adequately studied by anyone. Romberg[1] believes that the work of the left ventricle is enormously increased in changing from an arterial system with slight rigidity to an arterial system with great rigidity, and that therefore the work of the left ventricle must be increased in generalized arteriosclerosis. We have never been able to find a detailed description of Romberg's method and his experimental results.

Romberg's assistant Lange[2] has weighed hearts in cases of generalized arteriosclerosis and found little or no increase in weight, a bit of evidence which would seem to point to arteriosclerosis as no factor in increasing the work of the left ventricle.

After a brief survey of the field, we were convinced that a systematic investigation of the hemodynamics of arteriosclerosis was needed. We shall report today on the results of our preliminary investigation in this field. In this paper we shall consider arteriosclerosis as an increase in the rigidity of the arterial system down to the capillary area. Any decrease in the effective lumen of this system would lead to high blood pressure and will not be considered in this paper. By means of an analytic study of the problem, we feel that we have made it seem very probable that a marked degree of generalized systemic arteriosclerosis will not increase the work done by the left ventricle[3] provided the blood pressure does not rise. In

*Presented before the American College of Physicians, Minneapolis, Minnesota, February 11, 1930.

†From the Department of Medicine of the University of Minnesota and the Minneapolis General Hospital.

order that this latter condition be realized, we must provide that the arteriosclerosis or increased rigidity of the arterial system be produced in such a way that lumen changes are not produced at the same time that rigidity changes are produced.

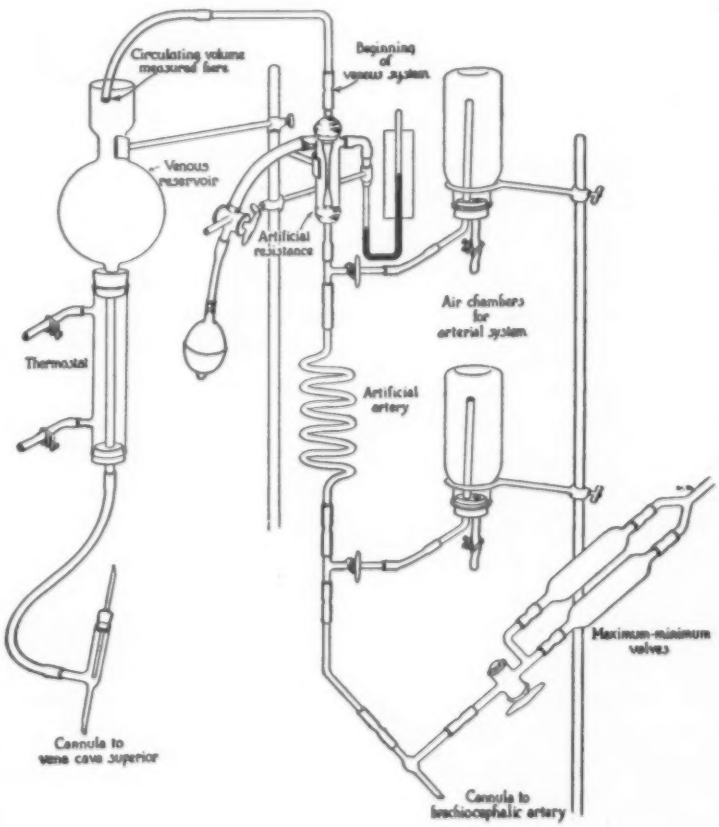
For all practical purposes the work which the left ventricle performs can be expressed in the form of an integral $\int_{p_0}^{p_1} P \, \Delta v$ which says that the work of the left ventricle is equal to the summation of the various small amounts of blood that are put out in a small time interval from the beginning of systole to the end of systole and against a blood pressure which rises from the diastolic to the systolic value. If the minute volume is kept constant, it can be easily seen that the only other factor in the work of the heart is the blood pressure. If we therefore keep the mean blood pressure constant or the systolic blood pressure constant, it can be easily seen even by the mathematical uninitiated that the work of the heart in arteriosclerosis is not going to be much greater than that in the normal condition so long as we assume that the output of blood from the heart per beat delete remains the same.

Making use of the data obtained by A. V. Hill[4] and the curve showing the relation between volume of the arterial system and blood pressure developed by Hill in his work, I have been able to integrate the work formula of the heart both for the normal artery and an artery with the rigidity three and a half times the normal. This integration shows that the work of the heart is just about the same in arteriosclerosis as in the normal condition, provided the output per beat remains the same and the arithmetical mean blood pressure remains the same. In this analytical method of attacking the problem, there was one factor about which we know nothing and which could not be taken into consideration, namely the "run off" from the arterial system. By making assumptions as to the time relations of the run-off, the A. V. Hill curve for the relation between volume of the artery and blood pressure could be reconstructed and then integrated, but this method was so full of assumptions that we believed it to be more convincing to work experimentally upon this problem. We have now finished our preliminary experiments and we can state definitely that if the minute volume of blood flow is kept constant and the arithmetical mean pressure remains the same, a very enormous degree of rigidity of the artery does not increase the work of the left ventricle. Moreover, we can state that under the given conditions the output of blood through the systemic circulation remains practically the same when the rigidity of the arterial system is increased many times. There is no dilatation of the heart in arteriosclerosis and the only adverse factor that we have so far been able to make out is a slight reduction of the flow of blood through the coronary arteries of the dog's heart in arteriosclerosis in some of our experiments.

A brief description of our experimental method is necessary for an understanding of the way in which the

problem was solved and will be given here.

The heart of the dog in a Starling Heart-Lung Preparation was used as pump. A cannula was inserted in the arch of the aorta of this heart, all arterial branches were ligated so that blood pumped out of the left heart was all forced through the cannula which was connected to a manometer and a system of tubes which emptied into a venous reservoir connected to the superior vena cava. The inferior vena cava was ligated. All the blood entering the superior vena cava from the reservoir passed into the right auricle, hence to right ventricle and through the lungs to the left ventricles. (See figure 1.) An artificial resistance is inserted in the arterial system, by means of which the blood pressure can be adjusted to any desired height and kept constant. The greater part of the arterial system consists of a coiled glass tube, with side tubes, provided with cocks and leading into two bottles each of 1,000 cc. capacity. When the passage to these bottles is closed the arterial system has a very high degree of rigidity, approximately 10 times the volume rigidity of the normal human arterial system as de-



termined by A. V. Hill et al. This degree of rigidity is much higher than the greatest rigidity measured by Hill on an old man with arteriosclerosis. The glass tube is of course extremely rigid. The manometer for measuring blood pressure and the artificial resistance are the only parts of the system that expand under pressure. In all measurements of the coefficient of volume elasticity of the arterial system, the artificial resistance and manometer were included. When the two cocks are opened the arterial system has two large air chambers which reduce the rigidity of the system to about one half the rigidity of a normal human arterial system, as determined by A. V. Hill. We were thus able to turn arteriosclerosis on and off at will by turning the stop cocks.

It has been shown by Starling and Vischer[5] that the diastolic volume of the heart is accurately proportional to the energy developed by the heart during each beat; that is the work of the heart per beat is determined exactly by the diastolic size of the heart; or in other words the diastolic volume of the heart is an accurate measure of the work of the heart provided the condition of the heart muscle remains constant. If the heart dilates more work is being done, if the diastolic volume gets smaller, less work is being done. In our experiments, the heart was enclosed in a cardiometer connected to a recording tambour designed by Wiggers. The tambour lever records the slightest variation in diastolic volume of the heart and thus indirectly records the work of the heart. If the heart does not dilate when the stop cocks are closed and the arterial system is rigid (arteriosclerosis) then we can be sure that this degree of arteriosclerosis does not increase the work of the left ventricle.

In addition we measured the volume flow of blood in the system circulation by allowing the blood from time to time to flow into a graduated cylinder. A stop watch graduated in 1/10 seconds was used to measure the time taken to fill the cylinder with a measured volume of blood. The minute flow could then be calculated. In this way the systemic minute flow in the rigid and non-rigid system could be measured with an accuracy of 5%. Moreover the cardiometer was calibrated by injecting a known quantity of air into the cardiometer and measuring the movement of the lever. We could then determine with some degree of accuracy the stroke output of the heart. In only one experiment did this value seem much too small, though in general this method of measuring stroke output is known not to be very accurate. Knowing stroke output, rate of the heart, and the systemic minute flow, the coronary flow is easily calculated. The rate of the heart remains constant in the rigid as well as non-rigid state, but because of the possible inaccuracy in the stroke output measurement, we do not lay much stress on our coronary flow figures. These must be checked by actual measurement in the future.

We append a selection from our experimental results to show that the work of the left ventricle is not increased during arteriosclerosis (rigid

*Experiment of April 16, 1929*

Rigidity of our material system with air chamber connection (normal) is 1/3 that of A. V. Hills "mean normal" human artery.

Rigidity of our arterial system without air chamber connection is 6.6 times "mean normal" human artery.

Ergo our system without air chamber connection is 20 times the rigidity with air chamber connection.

| | Without Air Chamber (Arteriosclerosis) | | With Air Chamber (No arteriosclerosis) | |
|---|---|---|---|---|
| Sys. B.P. | 246) | | 224) | |
| | ) | 120 | ) | 66 |
| Dias. B.P. | 126) | | 158) | |
| Stroke Vol. | 12.2 | | 12.7 | |
| Minute Vol. | 1220 | *Rate 100* | 1270 | |
| Circul. Vol. | *857* cc. | | *833* cc. | |
| Coronary flow | 363 | | 437 | |

The heart was about 1-1.5 cc. smaller in diastole when air chambers were not connected with arterial system; ergo no increase in work of heart in the more rigid arterial system. In fact less work was done in arteriosclerosis because stroke output and mean pressure were less. During the experiments with air chamber connected the flow from the tube leading into venous reservoir was steady with only a slight pulsation. During the experiments without the air chambers (arteriosclerosis) the blood spurted in jets from the end of the tube leading into reservoir. In some of our experiments the flow had nearly ceased at the end of diastole.

*Experiment of October 15, 1929*

Rigidity of arterial system with air chamber connected (normal) is 2/3 that of A. V. Hills "mean normal" human artery.

Rigidity of arterial system without air chamber connection (arteriosclerosis) is 10 times the rigidity of the "mean normal" human artery as determined by A. V. Hill.

Ergo the rigidity in our arterial system without air chamber connection is 15 times that of the arterial system with air chamber connected.

| | (Arteriosclerosis) | | | (No arteriosclerosis) | |
|---|---|---|---|---|---|
| | 126) | | | 122) | |
| Sys. B.P. | ) | 64 | | ) | 50 |
| Dias. B.P. | 62) | | | 72) | |
| Stroke Vol. | 7.5 | cc. | | 7.8 | cc. |
| Minute Vol. | 937 | cc. | | 975 | cc. |
| Circul. Vol. | *893* | cc. | *Rate 125* | .*857* | cc. |
| Coronary flow | 44 | cc. | | 118 | cc. |

Heart was dilating continuously from start of this set of experiments. Apparently no difference in diastolic volume without air chamber and which air chamber in arterial system.

*Experiment of Dec. 30, 1929*

Rigidity of our arterial system with air chamber connection (normal) is 3/4 the rigidity of A. V. Hills "mean normal" artery.

Rigidity without air chamber (arteriosclerosis) is 9 times the rigidity of the human arterial system as determined by A. V. Hill.

Ergo rididity in this artificial arteriosclerosis is 12 times the rigidity in the condition approximating normal.

| | With Air Chamber (Normal) | | Without Air Chamber (Arteriosclerosis) | |
|---|---|---|---|---|
| Systolic B.P. | 206) | | 192) | |
| | ) | 128 | ) | 88 |
| Diastolic B.P. | 83) | | 104) | |
| Circul. Vol | 1915 | cc. | 2000 | cc. |
| Stroke Vol. | 14.4 | cc.? | 14.2 | cc.? |
| Rate of Heart | 100 | | 100 | |
| Minute Volume | 1440 | cc? | 1420 | cc.? |
| Coronary Flow | —— | | —— | |

Diastolic volume is 0.8 cc. less without air chamber than with air chamber. In other words no increase in volume but rather a slight decrease in the condition of increased rigidity. Cardiometer values for stroke volume of heart are much too low. Probably due to improper position of cardiometer on heart. Minute volume must be about 2400 cc. This heart is doing nearly as much work as the heart of an athlete in severe exertion. The minute volume as well as the blood pressure is increased beyond the normal. Even under these circumstances the heart does not dilate during the period when it is pumping through the rigid system nor is the volume of the systemic circulation reduced.

system), and that the systemic minute volume remains practically constant whether the heart pumps into a very rigid arterial system or into a system which has air chambers.

These experiments prove that increased rigidity of the arterial system without changes in the diameter of the system causes no increase in the work of the left ventricle in expelling blood into and along the more rigid arterial system. In other words arteriosclerosis not associated with increased blood pressure causes no increase in the work of the left ventricle.

These experiments also prove that the volume flow of blood in a more rigid arterial system is as great as in a less rigid system. In other words arteriosclerosis not associated with narrowing of the lumen of the arterial system is not detrimental to the volume flow of blood.

It is possible that severe generalized arteriosclerosis may lead to a reduction in volume flow through the coronary arteries and thus aid in bringing on circulatory failure when the coronary arteries are already narrowed from severe coronary arteriosclerosis.

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# Some Newer Aspects in the Problem of Essential Hypertension*

NORMAN M. KEITH, M.D., *Division of Medicine,* and
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BRIGHT, 100 years ago, showed that there was a relationship between pathologic changes in the kidney and diffuse vascular disease. Forty years later, Johnson, Gull, and Sutton demonstrated in cases similar to those cited by Bright that there might also be injury to the peripheral vessels including the arterioles. Thirty-five years ago Allbutt showed clinically and pathologically that diffuse vascular disease with hypertension, without renal lesions, and without gross peripheral vascular lesions, could exist.

Since that time, of course, many observers have wondered as to the cause of hypertension, and there have been theories that the thyroid gland and the suprarenal gland were involved. In the last few years certain anatomic conditions of the vascular system have been recognized as being associated with hypertension. Much has been learned concerning the diagnostic and prognostic significance of retinal vascular changes. Moreover, certain rare conditions of the vascular system have come to be recognized as causative of hypertension. These include arteriovenous aneurysm and congenital stenosis of the isthmus of the aorta.

There are eight types of hypertension. The first is the hypertension of arteriovenous aneurysm; the second that associated with congenital stenosis of the aorta. Third, is the hypertension that occurs in hyperthyroidism, which disappears often with removal of a portion of the overactive thyroid gland. Fourth, is the very interesting condition, paroxysmal hypertension, that has come to the notice both of pathologists and of clinicians within the last few years. In the present study, the term "paroxysmal hypertension" is limited to those cases in which the hypertension appeared periodically and in which tumors were found in the region of the suprarenal gland. Fifth is the hypertension that is associated with eclampsia, or, as some like to call it, the acute glomerulonephritis of pregnancy. Then comes the subdivided group which Allbutt particularly stressed, essential hypertension. For want of better terms, the subsidiary types of essential hypertension are called benign, severely benign or early malignant, and malignant.

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A boy whom we had as a patient, had definite hypertension, with a systolic blood pressure of 185 millimeters of mercury, and a diastolic pressure of 80. He had an arteriovenous aneurysm which involved the femoral artery and femoral vein. When the abnormal connection between artery and vein was excised the blood pressure returned to normal.

Another patient, a man, had congenital stenosis of the isthmus of the aorta. He entered the hospital with a diagnosis of chronic glomerulonephritis. It was interesting to note the large superficial arteries between his scapulas. Woltman and Shelden, who have been much interested in such cases for many years, were of the opinion that the main condition was the stenosis of the aorta. At one time the patient had distinct hypertension with a systolic blood pressure of 205 and a diastolic pressure of 120.

In a case of exophthalmic goiter the basal metabolic rate was +80. Use of iodin and subsequent removal of a portion of the gland caused return of the basal metabolic rate and blood pressure to normal. One of the striking features of hypertension with hyperthyroidism is the marked increase in the pulse pressure.

The first case of paroxysmal hypertension that was thoroughly described was reported by Labbé in 1922. The patient was a young woman who had crises associated with marked hypertension. At necropsy a tumor was found which apparently arose from the suprarenal gland and it was felt had a causal relationship to the attacks of severe hypertension. Since the time of Labbé's report several cases have been noted in this country[9]. In three such cases a tumor was suspected, operation was advised and was carried out, and the tumor was removed. Apparent recovery and disappearance of the hypertension supervened.

One of these three cases, reported by C. H. Mayo occurred in a woman, a music teacher, of thirty years of age. One of us (Keith) saw this patient. The attacks of paroxysmal hypertension lasted from a half hour to three hours. They were very severe, and if they had continued to occur indefinitely the termination would have been fatal. After removal of a suprarenal tumor, which was reported to be a malignant blastoma, the blood pressure became and remained normal.

In the second case, reported by Pincoffs, the tumor was composed of chromophil tissue simulating that from the medulla of the suprarentl gland. In the third case, in which one of us (Keith) saw the patient before operation, the tumor was removed by Porter. The tumor apparently arose from the cortex and not from the medulla.

Wagener has described arteriolar spasm in the retina in eclampsia or acute glomerulonephritis of pregnancy, and has pointed out its importance. In this condition, vascular phenomena are associated with hypertension. This condition is illustrated by the case of a woman twenty-six years of age, in her first pregnancy, with a blood pressure as high as 180 systolic and 105 diastolic. After delivery the blood pressure dropped to normal and remained so, and three and a half years later a normal pregnancy occurred without any rise in blood pressure. In eclampsia, then there is a condition of acute

hypertension, and some of the changes that have been noted in the retinal arteries indicate that the condition which begins in the course of eclampsia possibly progresses from the acute to the chronic type.

In one case there was marked hypertension and marked toxemia of pregnancy, associated with very marked retinitis. Subsequently chronic vascular disease developed. The vascular condition may have been present before pregnancy; but after it became severe the blood pressure remained high and the condition in the arteries gradually became more marked. The patient died of cerebral hemorrhage, but at the time of postmortem examination any very definite renal injury was not found. This goes to show that in a certain group of cases of eclampsia in which the vascular condition progresses the residual lesion may be vascular rather than renal.

A number of cases of essential hypertension have been studied. One woman, for instance, has been watched for several years. In 1917 she had a very high blood pressure, 240 systolic, and 135 diastolic. Her blood pressure has remained practically the same since then. We have seen her within the last few months, but we have not seen actual retinitis. The cardiac and renal functions have remained good. This case, therefore, is of the benign type.

In the group of cases of essential hypertension, the benign type is much the commonest. It is a hopeful aspect in these cases, that there is a benign type and that it is much more frequent than the malignant type.

In 1920 a woman, aged thirty-nine years, went to the oculist for glasses and her ocular fundi were reported to be normal. Two years later she had marked hypertension. We have been able to follow this case closely since 1922. Retinitis began to develop in 1926 and periodically, particularly within the last few weeks, it has been marked. The changes are not those seen in malignant hypertension. Nevertheless the patient has high blood pressure, diffuse vascular disease, and recurrent retinal lesions. To our way of thinking these features indicate that the condition is more severe than that in a case of benign hypertension. This patient's condition is classified as severe benign or early malignant hypertension.

In a case of malignant hypertension which finally came to necropsy, in addition to the high blood pressure there were evidences of myocardial injury. There was no evidence of severe renal injury, and yet the retinitis was typical of malignant hypertension. The patient died of a cerebral hemorrhage. There was marked thickening of the arterioles in many organs, including the kidney, and yet the glomeruli and the tubules appeared to be in splendid condition. This case, then, is one of malignant hypertension.

In eighty-one cases of malignant hypertension which we have studied thoroughly, it is evident that the condition is not a disease of old age; it is a disease of youth and middle age. We have had patients as young as eight years of age but the great majority are aged between thirty and fifty years.

In one of our malignant cases which came to necropsy the arteriolar lesions in the kidney were marked. There

were similar marked changes in the wall of an artery which was seen in a section of skeletal muscle. Changes were found in arteries of the retina, the brain, the meninges, and in the coronary artery. That is, there were diffuse pathologic changes in the arterioles. The lesions of malignant hypertension that one of us (Kernohan)[5,6] has stressed are hypertrophy in the media, and in some cases also intimal thickening. The finding of these changes in the intima and media led us to see if we could not get some idea as to the condition of the arterioles in the living patient. Therefore, we have now carried out biopsy of the pectoral muscle in some 100 cases. Definite decrease in the lumen has been noted, in addition to the changes in the wall in a number of these cases. In a normal small artery or arteriole the ratio of lumen to width of the wall is about two to one. In a case of longstanding benign hypertension with general arteriosclerosis there is likely to be some thickening of the walls of arterioles. It may not be marked, and the ratio of wall to lumen, in our series, averaged 1 to 1.6. In a small artery from one of our cases of severe benign hypertension there was more thickening and some increase in the number of intimal cells. In this the ratio of wall to lumen was 1 to 1.4.

There is variation in this change of the ratio of the lumen to the thickness of the wall. In normal persons it varies from 1 to 1.5 or 2.5, averaging about 1 to 2. In benign cases the ratio averages 1 to 1.4. In our malignant, and in our severe benign or early malignant cases the ratio often approached 1 to 1.

In summing up, it behooves us as clinicians always to consider the diagnosis of a case of hypertension from the standpoint of the fundamental pathologic change. There are certain rare anatomic changes in the vascular system which give rise to hypertension, such as arteriovenous aneurysm and congenital stenosis of the isthmus of the aorta. In addition to the kidney we must think of other organs in the body as possibly being associated with the cause of hypertension. For instance, we must think of the thyroid gland and of the suprarenal gland together with tumors in the region of the latter. Also, we must think of the sympathetic nervous system, for vasoconstriction sometimes occurs in early cases of hypertension. Cases have actually been seen in which the condition has begun with vasoconstriction and in which, later, arteriolar thickening has appeared. Finally we must seek substances which will be effective in prevention of this vasoconstriction, or in its treatment when once it has developed.

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# Retinal Vascular Changes in Hypertension*

By Henry P. Wagener, M.D., *Section on Ophthalmology, The Mayo Clinic, Rochester, Minnesota*

A MERE catalogue of the changes observed in the retina of patients with hypertension offers little of interest to the internist. The presence of arteriosclerosis or of arteriolosclerosis and its complications, and of retinitis, is universally recognized. From the standpoints of differential diagnosis and prognosis, retinal changes are of definite value. But the most alluring possibilities offered by the retina seem to me to lie in the field of interpretation of the basic pathologic and the pathologicophysiologic changes concerned in the production of hypertensive disease, or, at least, of some of its more serious manifestations.

In my opinion, all of the branches of the central artery usually studied with the ophthalmoscope are arterioles. Visible sclerosis of these vessels, not secondary to primary disease of the optic nerve, of the retina, or of the choroid coat, is practically always evidence of hypertensive disease, whether or not the readings of blood pressure are high at the time of examination. The recognition of this fact is of importance, especially in the differential diagnosis of the types of myocardial degeneration, as has been pointed out by O'Hare and Walker, and by Yater and Wagener. In spite of some variations in the results of statistical studies, I believe that a majority of patients with hypertension of the essential type have some sclerosis of the retinal arterioles, although this sclerosis may be minimal. If the changes in the retina are confined to mild narrowing of the caliber of the arteries, or to mild arteriosclerosis, and if these changes do not increase in severity after observation for a reasonable length of time, the hypertension ordinarily may be assumed to be benign. In the more severe forms of hypertension, sclerosis is practically always present and progressively increases in grade. Advancing sclerosis of the retinal arteries, in my opinion, always implies potentially dangerous hypertension, whether or not the sclerosis is complicated by episodes of retinitis. Even senile persons, with benign hypertension of low grade, have slight, but unmistakable, evidences of hypertension and sclerosis in the retinal arteries. In other varieties of hypertension, such as that accompanying exophthalmic goiter and coarctation of the aorta, retinal arteriosclerosis is rarely seen; nor is it found in association with glomerulonephritis unless or

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until the nephritis is complicated by the development of a diffuse vascular lesion. It has been demonstrated clearly that sclerosis of the retinal arterioles, not secondary to local disease, is part of a similar degree of sclerosis of the arterioles throughout the body. Hence, in a case of hypertension, the presence of such sclerosis of the retinal arterioles, even if it is associated with retinitis, means that this hypertension is the result, or is a symptom of, a diffuse vascular lesion and is not secondary to primary glomerulonephritis.

In the literature numerous classifications have been given of the types of retinal vascular lesions and retinitis seen in association with hypertension. It is almost universally admitted now that the occurrence of retinitis in cases of hypertension does not necessarily imply renal involvement. If exception is made of the possible relation of eclampsia to nephritis, the various forms of retinitis observed in cases of glomerulonephritis do not enter directly into this consideration. Exclusive of these, the retinitis which occurs in hypertension may be divided satisfactorily into those dependent on local vascular disease and those originating in, or at least associated with, vasoconstriction, the angiospastic retinitis of Volhard. To the first group belong isolated hemorrhages in the retina, thrombosis of individual retinal veins with resultant hemorrhage, edema and exudation into the retina, and the retinitis of arteriosclerosis. Essentially, these are all strictly localized lesions and their diagnostic and prognostic significance does not differ greatly from that of the associated and usually causative arteriosclerosis. The observation of the course of venous thrombosis in the retina affords an opportunity for the study of the processes of vascular repair. Noting the rapidity and completeness of the compensation for the thrombosis through the formation of anastomotic circulation may perhaps afford a clue to the flexibility of the general vascular system. As a rule the healing is slower and less complete in older patients, but the degree of the associated arteriosclerosis also seems to be a factor in determining the outcome. The retinitis of arteriosclerosis is observed only in the presence of rather severe arteriosclerosis. Such patients are apparently especially subject to cerebrovascular accidents.

These localized types of retinitis should be carefully distinguished from those more generalized or diffuse types of involvement of the retina dependent on arterial constriction. The latter types of involvement always indicate progressive hypertension, and the rapidity or severity of the progression seems to be aligned with the degree and the generalization of the vasoconstriction as indicated in the retina by the extent and distribution of edema, hemorrhage, and exudation. The severity of the associated arteriosclerosis has no bearing in evaluating the prognostic significance of this retinitis, although it may afford a clue to the previous duration of the hypertension. It is possible to distinguish two distinct forms of this retinitis: one is associated with relatively benign hypertension, and the other with the ma-

lignant hypertension of Keith, Wagener, and Kernohan.

The predominant and the most interesting vascular feature of the retinal picture in the severe and rapidly progresive forms of hypertension unquestionably is arterial constriction. It is striking in the severe type of retinitis, but it is more readily studied when it is seen before the onset of retinitis. In any case in which hypertension is rapidly rising, it is the first visible change in the retinal vessels and it is definitely spastic in nature. As Haselhorst and Mylius have pointed out, the best opportunity for the study of this angiospastic process is afforded by cases of hypertension in toxemia of pregnancy. The first response visible in the retinal arteries in such cases is generalized narrowing of the blood stream. This is followed by more advanced narrowing of the arteries in localized spots or in individual branches. That these segments of advanced narrowing are produced by spasms is made evident by their shifting in situation and in degree. If the rise of blood pressure continues, the areas of constriction gradually become more extensive and more persistent in situation and duration and may be almost obliterative. From a comparative study of the retinal arteries and the capillaries of the nailfold, Haselhorst and Mylius expressed the belief that, when these spasms become definitely localized in a given situation, and are of sufficient duration and severity to produce stasis in the capillaries, edema and hemorrhage, that is, retinitis appears in the retina. At first, this retinitis is localized to the areas of most intense spasm; later, it becomes diffuse. This has been unquestionably the sequence of events in a number of cases of toxemia of pregnancy which have been closely followed. In the cases reported by Haselhorst and Mylius, the onset of eclamptic convulsions coincided in time with the appearance of maximal constriction of the retinal arteries.

In the retinas of these pregnant women, the amount of arteriosclerosis persistent after recovery from the acute toxemia seems to be definitely proportional to the persistence of the spastic constriction and to the resultant interference, through capillary stasis, with the nutrition of the walls of the vessel and of the retina. It has been my observation that the residual injury to the general vascular system in these patients is comparable to that found in the retina although that in the general system may be less in grade if severe retinitis has increased the local retinal arteriosclerosis through secondary changes. In any event, the majority of those who have definite residual sclerosis of the retinal arteries have persistent and usually progressive diffuse vascular disease.

In a few cases of an apparently essential type of hypertension, seen soon after the onset of what might be termed the acute phase of the hypertension, changes have been observed in the retinal arteries similar to the varying spasms seen in toxemia of pregnancy. Occasionally, these have been accompanied by scattered hemorrhages and mild edema of the retina. In cases of hypertension of longer standing, and with definitely visible

sclerosis of the retinal arteries, localized spasms are more difficult to demonstrate. In such cases, however, there are frequently seen scattered areas of retinitis, similar to those seen in the early stages of the retinitis of toxemia of pregnancy, and which may be assumed perhaps to be due to the same factors. This is the type of retinitis which I term the retinitis of severe benign hypertension. It is characterized by the addition to arteriosclerosis of scattered hemorrhages and white patches, pictorially described as cotton-wool exudates. Any striking vasoconstriction and any definitely visible edema of the retina are usually confined to the region of these hemorrhages or exudates. Such retinitis may appear in slight degree and transiently in relatively benign hypertension, but as a rule it is subject to periodic appearance or to recurrence, and the hypertension associated with it, must be regarded as relatively dangerous, although it is usually amenable to control, as is the retinitis itself.

The second type, the retinitis of malignant hypertension, is quite different. In this there is usually, and always in the early stages, distinct and generalized spastic constriction of the retinal arteries, in association with generalized edema of the retina, hemorrhages, cotton-wool patches and, particularly, hyperemia and measurable edema of the disk which may reach the height of 5 to 6 diopters. The macular stars featured in many descriptions of retinitis are merely later phases of edema of the retina and are not of diagnostic significance. The cause of the edema of the disk is not known, although it may be partially dependent on the increased pressure of the spinal fluid and the presumably increased intracranial pressure present in the majority of these cases. The outcome in cases of the typical retinitis of malignant hypertension is almost invariably fatal within a relatively short time, as Keith, Wagener and Kernohan have pointed out; very few of the patients live more than from eighteen months to two years. The retinitis usually persists in spite of treatment and the hypertension itself does not yield satisfactorily to any measures for its control.

As is to be expected, there are apparently some cases of rapidly progressive hypertension in which this typical retinitis is not seen. This is particularly true of patients who present themselves first with severe cardiac decompensation, in whom, perhaps, the capability of intense vasoconstriction is absent. In such patients, the retina gives evidence only of arteriosclerosis or at most of retinitis of a severe benign type. There are other patients who may belong in the group of malignant hypertension, whose retinitis is essentially of the severe benign type except that there is mild, diffuse edema of the retina sufficient to cause some blurring of the margins of the disk but without any definite swelling of the disk itself. There is some evidence to show that persistently recurring retinitis, of the severe benign type, may ultimately assume this form. Such patients I have tentatively placed in a borderline malignant or intermediate group. The exact prognostic significance of this type of

retinitis has not as yet been definitely determined. In a few cases, typical retinitis of malignant hypertension has resolved more or less completely and has shown no tendency to recur. Although a few of these patients have done well for a considerable period, as a rule the disease progresses to its usual rapidly fatal outcome in spite of the healing of the retinitis. Hence the fact that in certain cases the retinitis may be observed for the first time in its healed or residual stage does not alter the severity of its prognostic significance.

If it can be assumed, then, as seems justified by the histologic studies of Keith, Wagener and Kernohan, that the same processes observed in the retina are going on in the arterioles throughout the body, it must be admitted that arterial constriction or spasm is the most dangerous element of hypertensive disease, that it may be the primary factor that results in arteriosclerosis, and that it is largely responsible, if not for the hypertension itself, at least for the retinal, cerebral and renal complications. It would seem that efforts should be directed especially to the discovery of the cause and to the relief of this tendency to arterial, or rather to arteriolar constriction.

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# The Causes of Hypertension*†

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THIS paper deals with the various factors that regulate or influence blood pressure in health and disease. By a study of known processes we may approach the problem of primary hypertension.

A. Mechanisms concerned in the regulation of the blood pressure.

1. *The heart.* The energy required to maintain or elevate the systemic blood pressure is furnished by the contraction of the left ventricle. When the peripheral resistance is increased the blood pressure must be raised, if the tissues are to receive as much blood as they did before the increase of resistance occurred. When the tissues require more blood, as during violent exercise, an increase of blood pressure is needed to force the blood through the vessels more rapidly. The heart raises the blood pressure by stronger or more frequent contractions. A compensatory hypertrophy of the left ventricle occurs when the functional demand upon the heart persists for some time.

A strong myocardium is necessary for the maintenance of a high blood pressure. When the nutrition of the muscle is lowered by disease of the coronary arteries or general malnutrition, the heart may be unable to keep the blood pressure at a high level, even though peripheral resistance is increased. A large heart that has maintained a high blood pressure for years may finally become exhausted and allow the pressure to become subnormal.

The heart suffers more than any other organ from the effects of hypertension since it is exhausted by overwork; but hypertension is not a primary disease of the heart. The blood pressure is not elevated unless the resistance in the arterial system is increased. There is no increased output of the heart in hypertension.

2. *The small arteries and arterioles.* The peripheral resistance depends upon the degree of contraction of these vessels. Their tonicity is regulated by the vasomotor center through the vasomotor nerves. When the vasomotor center is disconnected, as by section of the cervical spinal cord, there is a generalized dilation of small arteries and arterioles and a marked decrease of blood pressure. When the vasomotor nerves to any particular organ, e.g., the ear of the rabbit, are

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sectioned the blood vessels dilate immediately and the organ remains congested for weeks or months, but the vessels finally regain their tone. Stimulation of the vasomotor center causes a generalized contraction of small arteries and arterioles and a rise of blood pressure.

A generalized contraction of the arterioles is necessary to increase the peripheral resistance. When the vessels of one organ only are constricted a slight relaxation elsewhere will prevent an increase of resistance.

Even in the most extreme cases of arteriolosclerosis only a relatively small percentage of the arterioles show organic changes. The arterioles of the skeletal muscle, skin, bones, heart, lungs, and intestinal tract seldom show any microscopic evidence of disease. It follows then that spastic rather than organic constriction of the arterioles is the chief cause of increased peripheral resistance.

But organic disease of the arterioles of a single organ may cause hypertension indirectly through a reflex mechanism. Evidence will be presented in subsequent paragraphs to show that obstruction of arterioles in the brain and in the kidneys causes a rise of blood pressure.

3. *The capillaries.* In occasional instances the condition of the capillaries influences blood pressure. In certain forms of shock there is a widespread capillary dilation. The greater part of the circulating blood collects in the distended capillaries, and the arterial pressure consequently falls to a very low level. This type of shock occurs particularly when there is opportunity for the absorption of toxic substances from large masses of necrotic tissue, e.g., in infarction of the intestine. It is believed that the capillary paralysis is due to histamine poisoning, since a similar condition may be produced experimentally by injections of histamine.

There is no known disease of the capillaries which causes an increase of blood pressure.

4. *The vasomotor center.* This center regulates the tone of the small arteries and arterioles and in this way controls the blood pressure. It is influenced by stimuli of various kinds. Increased intracranial pressure causes rise of blood pressure, probably through anemia of the vasomotor center. Stimulation of sensory nerves, such as occurs in severe pain (gastric crisis of tabes, lead colic, acute cholecystitis, etc.) causes a sharp rise of blood pressure. Emotional disturbances (fear, anger, worry, etc.) may cause a rise of blood pressure. Stimulation of the central end of the depressor nerve causes a decrease of blood pressure. It is possible that substances in the circulating blood affect the vasomotor center, but none such are definitely known. Continuous stimulation of the vasomotor center probably occurs in nearly all forms of secondary hypertension and may be present in the primary form.

5. *The vasomotor nerves.* These nerves transmit impulses from the vasomotor center through the sympathetic ganglia to the muscle fibers of the blood vessels. The arteries relax when their vasomotor nerves are severed. Adrenalin stimulates the termi-

nations of the nerve fibers in the smooth muscle of blood vessels, causing spasm of the arterioles and a rise of blood pressure. Hyperirritability of the sympathetic nervous system is regarded by Kylin as the basic cause of primary hypertension. The only evidence in support of this hypothesis is obtained from a study of Raynaud's disease. In this condition there is a spastic contraction of the arteries of the lower extremities which is relieved by lumbar sympathetic glanglionectomy. Inasmuch as the blood vessels show no organic disease, the condition may well be regarded as due to overstimulation of the sympathetics. However, there is no hypertension in Raynaud's disease, the vascular spasm being restricted to relatively small areas of the body.

6. *The depressor nerves.* These nerves are branches of the vagi that supply the ascending arch of the aorta. Stimulation of the central end of the sectioned nerve causes a fall of blood pressure. It is believed that an increase of blood pressure in the aorta stretches the wall of the vessel, thereby stimulating the depressor nerves. Hering and his associates have shown that complete removal of the depressor nerves in the rabbit is followed by a persistent elevation of blood pressure.

7. *The adrenals.* There are three lines of evidence which indicate that the adrenals are concerned in the regulation of blood pressure. (a) It is well known that extracts of the medulla cause a sharp temporary rise of blood pressure when injected subcutaneously or intravenously. (b) In Addison's disease, in which the adrenal tissue is largely destroyed by tuberculosis or simple atrophy, the blood pressure is usually subnormal. However the blood pressure is sometimes normal and rarely there is a definite hypertension. (c) Certain malignant tumors of the adrenals are characterized by paroxysmal hypertension, and one case is reported (Vaquez, Donselot, and Géraudel) in which the intermittent paroxysmal hypertension finally passed over into a continuous hypertension.

On the basis of these facts many investigators have suggested that primary hypertension is caused by overfunction of the adrenals. But biochemical researches do not support this view, and there are no evidences of hyperplasia of the adrenals in primary hypertension.

B. Experimental hypertension.

1. *Injection of various pressor substances causes a transitory hypertension.* The best known of these are adrenalin, pituitrin, ephedrin, and methyl guanidin. The hypertension produced is of short duration, and repeated injections do not result in chronic hypertension.

2. *Increased intracranial pressure.* In Cushing's classic experiment a cannula was inserted into the subdural space through a watertight opening in the skull and conected with a beaker of normal salt solution. The intracranial pressure was varied by raising and lowering the beaker. The intracranial pressure and the blood pressure were recorded simultaneously by mercury manometers. When the intracranial pressure was raised above

the level of the blood pressure a sharp rise of the latter occurred.* This reaction did not take place after sectioning of the cervical spinal cord. Cushing considered the rise of blood pressure due to anemia of the vasomotor center.

3. *Removal of the depressor nerves.* Koch and Mies produced chronic hypertension in rabbits by complete removal of the depressor nerves. In cases of long standing, arteriosclerosis of the aorta of the adrenalin type results. Hering believes that the function of the depressor nerves is to inhibit the secretion of adrenalin, and that the rise of blood pressure is due to increased secretion of adrenalin.

4. *Experimental renal lesions.*

(a) Urinary obstruction. In one of our experiments a male rabbit developed acute obstruction of the urethra following repeated catheterization. The blood pressure rose about 40 mm Hg 24 hours later. A similar hypertension was obtained in another rabbit by ligature of the penis.

(b) *Röntgen ray atrophy.* Hartmann produced marked atrophy of both kidneys in dogs by radiating the kidneys. The animals developed hypertension and uremia.

(c) Pedersen produced severe chronic passive congestion of one kidney in rabbits in the following manner. The left renal vein is carefully dissected out and surrounded by a heavy aluminum wire. The wire is then compressed about the vein until only a small lumen is left. Care is used not to occlude the vein completely. The kidney immediately becomes swollen and cyanotic. If the constriction of the vein is too great a hemorrhagic infarct develops and the experiment fails. The kidney is removed from its bed and then covered completely with a thin membrane which is drawn snugly about the hilus. (Fig. 1) It is then replaced and secured by sutures. The membrane prevents the development of collateral circulation. If the kidney is not put inside a membrane, a collateral venous circulation develops rapidly and the passive congestion disappears within a few days.

*See McGregor, L., Arch. Path., 1928, V, 657, Fig. 9.

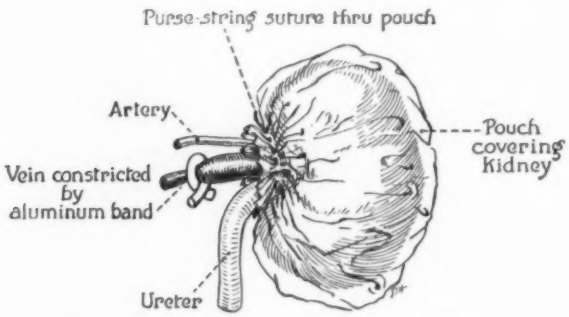


Fig. 1. Diagram illustrating a method of producing permanent venous congestion in the kidney.

By this procedure the kidney is kept distended, its capsule is tense, and the resistance to the flow of blood through it is greatly increased by the venous obstruction. After the operation the blood pressure rises slowly and remains well above the normal level for about two months, after which time it returns slowly to normal. (Fig. 2)

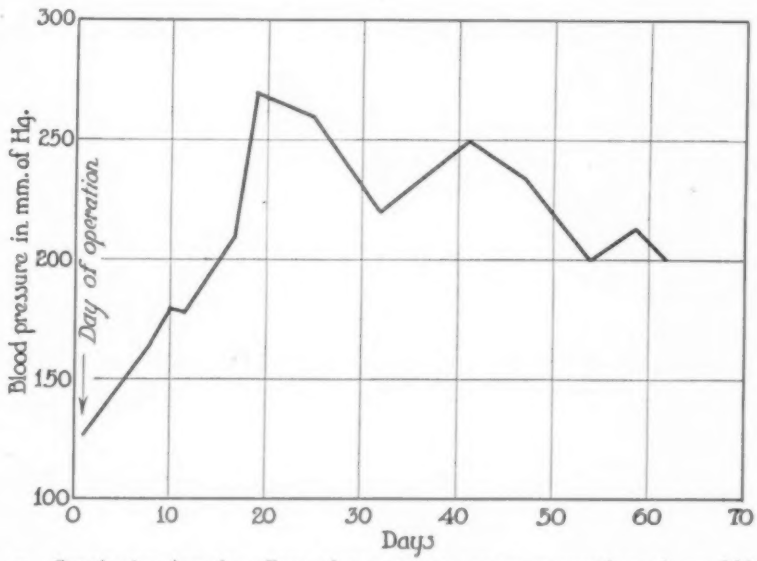


FIG. 2. Graph showing the effect of permanent venous congestion of one kidney upon the systolic blood pressure.

The kidney inside the membrane shows very striking changes. At the end of two months the capsule of the kidney has become enormously thickened and the parenchyma has undergone marked atrophy (Fig. 3). The capsular thickening is caused by the irritation of the surrounding membrane. The atrophy of the parenchyma is due largely to the extreme passive congestion.

The hypertension is presumably due to obstruction in the renal circulation, such as occurs in renal diseases in man.

C. *Secondary Hypertension in man.*

Hypertension is called secondary when it is caused by some known condition or disease. The different forms of secondary hypertension will now be described.

1. *Hypertension due to physical exertion.* The normal individual responds to undue physical exertion with a moderate rise of systolic and a slight fall of diastolic pressure. After a short rest the blood pressure returns to normal. The decrease of the diastolic pressure corresponds with a relaxation of the peripheral vessels. Both the systolic rise and the diastolic fall of pressure serve the purpose of bringing more blood to the tissues, particularly to the active muscles.

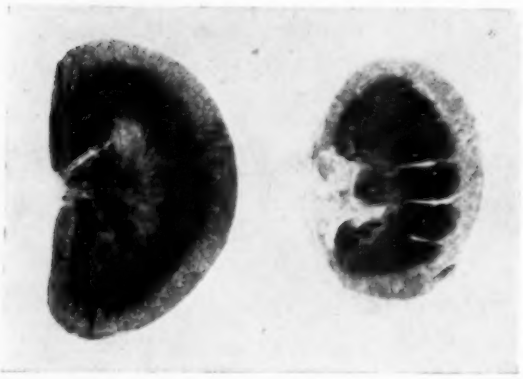

FIG. 3. a, normal kidney of rabbit; b, kidney after two months of venous congestion. Note thickening of capsule and atrophy of parenchyma.

An individual with chronic hypertension responds more readily than the normal person to physical exertion. The systolic pressure rises but the diastolic does not fall. Dyspnea develops more quickly and a much longer time is required for the blood pressure to return to its previous level (May, H).

2. *Hypertension due to sensory stimulation.* Intense pain such as lead colic, the gastric crisis of tabes, acute cholecystitis, etc., often causes a marked elevation of blood pressure which persists until the pain subsides.

In the same category belongs the hypertension of emotional disturbances (fear, anger, anxiety, etc). The elevated blood pressure persists only a short time. A person with chronic hypertension responds more readily to these stimuli than the normal, and some investigators believe that a hypersusceptibility to sensory stimulation is the basis of primary hypertension.

3. *Hypertension due to increased intracranial pressure.* Cushing's experiment has been described. In the usual case of apoplexy there is a massive local hemorrhage, but no uniform increase of intracranial pressure and no increased pressure on the medulla. This form of hemorrhage does not cause an increase of blood pressure; but when the blood spreads uniformly over the surface of the brain so as to compress the medulla the blood pressure increases. The majority of brain tumors do not cause a uniform increase of intracranial pressure and therefore do not cause hypertension. In an occasional case of primary hypertension the cerebrospinal fluid is under increased pressure, and a marked fall of blood pressure and improvement of symptoms follows spinal puncture.

4. *Hypertension due to adrenal tumors.* This topic has been discussed in a previous paragraph.

5. *Hypertension due to renal disease.* Secondary hypertension is found more frequently in association with diseases of the kidneys than with those of all other organs combined. It is evidently due to some change within the kidneys and not to the suppression

of renal function, since removal of both kidneys does not cause hypertension. Not all renal diseases result in hypertension. In general hypertension occurs in those in which there is obstruction to the blood flow, due to narrowing of the small arteries, arterioles, or glomerular capillaries.

The nephroses due to bacterial toxins do not cause hypertension. In these the renal injury is usually slight. Severe renal injury is found only in the terminal stages of infections when the circulatory system may be unable to react. The only chemical nephrosis in which hypertension has been reported is bichloride poisoning. Hypertension has never been reported in pyelonephritis or renal tuberculosis.

(a) *Glomerulonephritis.* Hypertension occurs in a large majority of instances of this disease. In mild acute cases it is not pronounced and may not be found if the patient is first examined several days after the onset. In mild chronic cases hypertension is often slight and may be absent. When the blood pressure is normal in glomerulonephritis it is usually safe to assume that the lesion is not severe. The important lesion in glomerulonephritis is swelling of the endothelium with narrowing and occlusion of the glomerular capillaries. In long standing cases the arterioles are also sclerosed and narrowed. There is obviously greatly increased resistance to the flow of blood through the kidneys.

(b) *The nephrosis of eclampsia.* Some of the toxemias of late pregnancy develop on the basis of a preexisting glomerulonephritis. These are called nephritic toxemia. The majority, however, develop in women who had no renal disease even during early pregnancy. These latter, which may be called simple toxemia, are characterized by high blood pressure, albuminuria, and edema. In fatal cases the kidneys are enlarged, very cloudy, and fatty. In four out of eight cases which we have examined there was a marked swelling of the glomerular endothelium with narrowing of the capillaries, i.e., an acute glomerulonephritis. In the other four cases no glomerular lesions have been demonstrated. All eight cases had hypertension.

(c) *Mercuric chloride nephrosis. In* this disease hypertension has been noted frequently during the final stage of anuria. There is extensive degeneration and necrosis of the tubules. The glomeruli show severe degenerative changes but no necrosis. It is probable that the blood flow through the glomeruli is impeded by the degenerating cells, but there is no definite proof of this.

(d) *Polycystic kidneys.* The available literature indicates that about one-half of the advanced cases of polycystic kidneys in adults have hypertension. There is presumably obstruction in the renal circulation in these kidneys, but it has not been determined whether there are any structural differences between those with hypertension and those with normal blood pressure.

(e) *Urinary obstruction.* Von Monakow reports a rise of blood pressure to 170 mm Hg due to an ureteral calculus. The blood pressure fell to 112 mm Hg after removal of the stone.

Braasch reports three cases of carcinoma of the uterus that had infiltrated the broad ligaments and compressed the ureters. The blood pressure would rise during the periods of anuria but would fall to normal when the obstruction was relieved. There are numerous reports dealing with the acute hypertension that follows urinary retention due to prostatic hypertrophy. The blood pressure falls sharply after the bladder is drained.

In urinary obstruction the urine is secreted against a high intrapelvic pressure. The rise of blood pressure aids in the filtration of fluid through the glomerular capillaries.

(f) *Advanced amyloid disease of the kidneys.* Hypertension is not found in amyloid disease except in some of the cases that progress to uremia. The blood pressure is not dependent upon the size of the kidneys. The difference, if any exists, between hypertensive and nonhypertensive types has not been determined.

(g) *Sclerosis of small renal arteries and arterioles.* There is a sharp difference of opinion among investigators as to whether sclerosis of the renal vessels is a cause or an effect of hypertension. The arguments in favor of the view that the vascular disease comes first are as follows: (i) In the great majority of chronic cases in which the cause is known (secondary type) hypertension is associated with disease of the kidneys. (ii) In fulminating cases of primary hypertension there is necrosis of arterioles and inflammatory changes in the glomeruli—processes which cannot be explained as a result of increased intravascular pressure. We cannot avoid the conclusion in cases of this type that the arteriolar and glomerular lesions are caused by some toxic substance and not by the increased blood pressure. (iii) Small areas of hyaline degeneration are often seen in the renal arterioles in acute glomerulonephritis Since the hypertension is of short duration and moderate intensity in this disease, it is more reasonable to interpret these as the effect of a toxin.

The chief argument in support of the view that hypertension is not caused by arteriolosclerosis is the fact that in about ten per cent of typical clinical cases of hypertension there are no anatomic changes in the renal arterioles. These cases differ in no way clinically from those with slight or moderate arteriolosclerosis; and we cannot therefore agree with Th. Fahr that the group with normal arterioles represents a different kind of hypertension. There are also many cases with only slight degeneration of the arterioles, which seem insufficient to cause much obstruction to the renal circulation unless we assume that arterioles that appear normal histologically are already rigid.

In long standing cases of chronic glomerulonephritis there is often a pronounced arteriolosclerosis in the kidneys. This is interpreted by Fishberg as evidence that prolonged hypertension causes arteriolosclerosis. However, it may be argued that the arteriolar degeneration is the effect of a toxin.

### Comment

From the foregoing discussion it is evident that acute hypertension may

be caused by unusual physical exertion, stimulation of sensory nerves, emotional disturbances, increased secretion of adrenalin, increased intracranial pressure with compression of the medulla, certain chemical substances (methyl guanidin, etc.), and urinary obstruction. The stimulus causing a rise of blood pressure may act by direct or by reflex stimulation of the vasomotor center, which results in increased peripheral tonus. The stimulus may also act directly on the smooth muscle of the vessels or on the nerve terminations in the muscle. Theoretically, widespread irritation of the sympathetic ganglia or vasomotor nerves would cause hypertension, but no clinical or experimental instances of this are known.

The only clinical examples of chronic hypertension, in which the etiology is known, are those caused by disease of the kidneys. A close study of renal diseases, in which hypertension occurs, reveals lesions of three types: (a) obstruction to the flow of blood through the glomerular capillaries (glomerulonephritis, toxemia of pregnancy); (b) obstruction in the arterioles (advanced amyloid kidney, fulminating hypertension); (c) increased resistance to the excretion of fluid from the glomerular capillaries (urinary obstruction). Experimentally a fourth type of lesion causing hypertension may be added, viz., obstruction to the outflow of venous blood (experimental stenosis of the renal vein).

The proper functioning of the kidneys is necessary for life, and the rise of blood pressure is a compensatory process adapted to the preservation of renal function under the abnormal conditions. When there is increased resistance in the renal circulation, the blood pressure must be increased in order to maintain the normal blood flow. In urinary obstruction an increase of blood pressure aids in the excretion of urine. By teleological reasoning we may conclude that afferent impulses pass from the diseased kidney to the vasomotor center and cause general vasoconstriction. However, such a reflex mechanism has not been demonstrated. Denervation of the kidneys in chronic glomerulonephritis with hypertension would determine whether such a reflex exists.

We do not know whether any of the causes of secondary hypertension are operative in the primary form, but the same mechanisms must be concerned in both types. In the early stages of primary hypertension the blood pressure falls to normal during sleep but returns to its previous level immediately upon awakening. This fact suggests that the vasomotor center is hypersensitive to sensory stimuli. In cases of long standing and especially when there is extensive renal involvement, the pressure does not fall during sleep.

A temporary fall of blood pressure is obtained with nitrites and other drugs more readily in the early stages of the disease than in the later stages, especially in those with extensive involvement of the kidneys. Either the arterioles become more rigid or the stimulation of the muscle is stronger and more constant in the later stages of the disease.

The narrowing of the arterioles over the greater part of the body is

spastic rather than organic. It is however theoretically possible that arteriolosclerosis of one organ, e.g., the kidney or the brain, may cause general vascular spasm by a reflex mechanism such as apparently occurs in secondary hypertension. In acute fulminating primary hypertension it is highly probable that the arteriolar and glomerular lesions antedate and cause hypertension. We cannot explain necrosis of arterioles and glomerulitis as a result of increased blood pressure.

In cases of primary hypertension with extensive involvement of the kidneys the blood pressure is usually at a higher level and more fixed than in other types. Renal arteriolosclerosis may owe its origin to hypertension, but when it has progressed to an advanced stage it has a striking effect in causing hypertension.

Renal arteriolosclerosis and hypertension are associated so frequently that there must be a casual relation between them. Either one causes the other or both are the effects of some unknown cause. In the light of our present inadequate knowledge, a tenable hypothesis is the following: Hypertension begins as a spastic condition of the arterioles which in certain organs, notably the kidneys, leads to arteriolosclerosis. In this way a vicious cycle is established, each condition aggravating the other. In the event that an infection supervenes the renal arterioles and glomeruli may be severely damaged, so that a fulminating hypertension with uremia develops.

No adequate explanation of primary hypertension has ever been offered. It is known that inheritance is of great importance. It is frequently observed in several members of a family. It is said to be very rare in the Chinese and in primitive African tribes. What is inherited is evidently an inferior vascular system which either reacts excessively to the environment or degenerates and becomes rigid from inherent weakness without the factor of overstimulation. It is largely a disease of advanced life. The cases that occur in young persons are usually of the renal type, and probably represent a primary renal disease.

In most instances of primary hypertension there is no adequate evidence that it begins as a renal disease. This question could probably be settled finally if some courageous surgeon would denervate the kidneys in a case of primary hypertension.

Occupation is without influence in the origin of hypertension, but excessive physical or mental strain may greatly aggravate an existing hypertension.

## Summary

The physiologic mechanisms concerned with the regulation of blood pressure in health and disease are discussed, viz., the heart, the arteries and the arterioles, the capillaries, the vasomotor center, the vasomotor nerves, the depressor nerves, and the adrenals.

Hypertension has been produced experimentally in animals by pressor substances, increased intracranial pressure, removal of the depressor nerves, urinary obstruction, röentgen-ray atrophy of the kidneys, and stenosis of the renal vein.

Secondary hypertension of acute type occurs in man from physical ex-

ertion, sensory stimuli, increased intracranial pressure, and adrenal tumors.

Secondary hypertension of acute or chronic type occurs with glomerulonephritis, nephrosis of eclampsia, bichloride nephrosis, polycystic kidneys, urinary obstruction, advanced amyloid disease, and degeneration of small renal arteries and arterioles.

Secondary hypertension of chronic type is seldom seen except in association with renal disease.

Obstruction in the renal circulation or obstruction of the outflow of urine seems to cause hypertension, probably through a reflex mechanism. Renal insufficiency alone does not cause a rise in blood pressure.

Acute fulminating hypertension is probably a primary renal disease.

Primary hypertension has its basis in inheritance. The defect inherited is an inferior vascular system which either reacts excessively to ordinary environmental stimuli or degenerates from inherent weakness.

References to the literature of hypertension may be found in: Bell, E. T. and Clawson, B. J. A study of 420 cases of primary hypertension. Arch. Path., 1928, v, 939-1002.

# Undulant Fever (Brucelliasis)*†

## A Clinicopathologio Study of Ninety Cases Ocurring in and About Dayton, Ohio

By Walter M. Simpson, M.S., M.D., F.A.C.P., *Dayton, Ohio*

Undulant fever is now recognized as a common disease of man. The knowledge of its widespread distribution, particularly in this country, is largely a development of the past two years. At a recent meeting of the Health Section of the League of Nations, it was stated that undulant fever is the most important problem facing public health workers at the present time. Prior to 1925, 128 cases of undulant fever had been recorded in this country. During the period from 1925 to 1928, the recorded cases numbered 24, 46, and 217 respectively; during 1928, largely due to the dissemination of information regarding the disease, 649 cases were recorded[1]. The writer has conducted a nation-wide survey of the number of cases of undulant fever recorded by state health departments during 1929; this survey reveals that 1301 cases, occurring in every state of the Union, were reported during the past year. This total of 2365 cases does not include the indeterminable number of cases which have been recognized as the result of confirmatory laboratory studies carried out in hospital and private laboratories, since not all state health departments list undulant fever as a reportable disease.

The writer has investigated 90 confirmed cases of undulant fever in and about Dayton, Ohio, during the past 18 months. The first 63 of these cases are reported elsewhere[2]. These findings were the result of a determined effort to learn of the incidence of the disease in a given locality. Hardy[3], activated by a similar motive, has investigated over 300 cases in Iowa. Carpenter[4] in New York, Huddleson[5] in Michigan, King[6] in New York, Bierring[7] in Iowa, Farbar and Mathews[8] in Indiana, Brown[9] in Kansas, Sensenich and Giordano[10] in Indiana, and Ey[11] in Ohio, have conducted similar investigations in their localities; their efforts have likewise been rewarded by the discovery of a large number of cases. The inference is obvious that the disease must be much more prevalent than is generally believed.

American physicians should derive great pride from the fact that the reawakening of international interest in this disease has been the direct result

*From the Diagnostic Laboratories of the Miami Valley Hospital, Dayton, Ohio.

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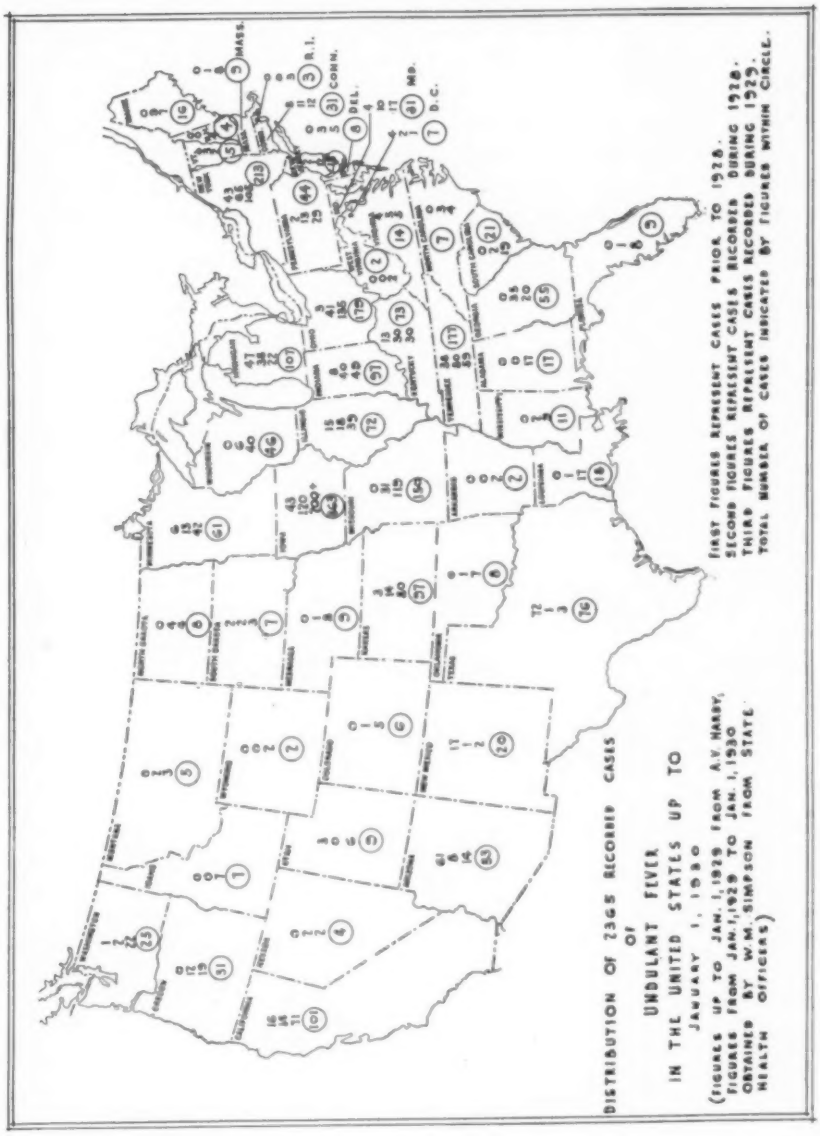
DISTRIBUTION OF 2365 RECORDED CASES OF UNDULANT FEVER IN THE UNITED STATES UP TO JANUARY 1, 1930
(FIGURES UP TO JAN. 1, 1929 FROM A.V. HARDY, FIGURES FROM JAN. 1, 1929 TO JAN. 1, 1930 OBTAINED BY W.M. SIMPSON FROM STATE HEALTH OFFICERS)
FIRST FIGURES REPRESENT CASES PRIOR TO 1928.
SECOND FIGURES REPRESENT CASES RECORDED DURING 1928.
THIRD FIGURES REPRESENT CASES RECORDED DURING 1929.
TOTAL NUMBER OF CASES INDICATED BY FIGURES WITHIN CIRCLE.

of the discoveries of American workers. The leader among these is Alice C. Evans[12], bacteriologist of the United States Public Health Service, who, in 1918, published the results of a comparative study of the organisms then known as *Bacillus abortus* of Bang, the cause of contagious abortion of cattle, and *Micrococcus melitensis* of Bruce, the etiologic organism of Malta fever. Evans had discovered that the two organisms were indistinguishable morphologically, biochemically, culturally and by ordinary agglutination reactions. She found that pregnant guinea pigs inoculated with either

organism produced the same percentage of abortions. Evans[13] also demonstrated that *Brucella melitensis* behaved exactly like *Brucella abortus* when injected into a pregnant heifer. Shortly after these discoveries, Fleischner, Vecki, Shaw and Meyer[14] found that *Brucella abortus* produced a disease in monkeys identical with that produced by *Brucella melitensis*. In 1927, Carpenter[15] recovered from the blood of 10 human beings with undulant fever an organism indistinguishable from the organism of contagious abortion; 5 pregnant heifers aborted promptly after inoculation with these cultures. For twenty years these two organisms had been regarded as separate, unrelated species. The remarkable observations of Evans have been confirmed by many workers in this country, Germany, Austria, France, England, Denmark, Italy, Netherlands, Egypt, Tunisia, and Japan.

*Terminology*

It became immediately apparent that a new terminology was indicated for these organisms. Meyer and Shaw[16] proposed that the *abortus-melitensis* group of organisms should be designated by the generic name *Brucella*, thus honoring Bruce, who discovered the Malta fever organism in 1887. Their suggestion has met with universal approval. Even though the caprine, and the so-called bovine and porcine strains of the organism are unquestionably serologic varieties of the same species, the name *Brucella melitensis* is generally used to designate the variety usually found in goats, while the name *Brucella melitensis* variety *abortus*, or *Brucella abortus*, has been applied to the variety found commonly in cows and hogs; the latter variety has been further divided by some writers into bovine (*bovis*) and porcine (*suis*) types.* Until it has been more conclusively demonstrated that the so-

*In a recent communication to the author, Doctor C. W. Stiles, Secretary of the International Congress on Zoological Nomenclatures has commented as follows in regard to the question as to whether the various types of *Brucella melitensis* should be considered as separate species:

"The difference between 'a species' and 'a variety' is purely subjective and this subjective difference of opinion varies not only among authors but also from time to time with one and the same author. In case of difference of opinion, two courses are possible, namely: (a) to consider two units as distinct species; this has the advantage of simplifying the nomenclature, for instance, *Brucella suis* in place of *Brucella melitensis suis*, or (b) to consider two units as varieties of one species; this has the advantage of showing closer relationship. Thus, to the uninitiated, *Brucella suis* does not show that this organism has any more than generic relation to *Br. melitensis* or *Br. abortus*, while *Br. melitensis suis* would indicate close relationship between *melitensis* and *suis*. This is of considerable practical importance, especially for authors who think of *Brucella* as a synonym of *Bacillus*. In the transitional stage of our knowledge of any units, experience shows that subgenera and subspecies permit a more conservative position than do genera and species, and in addition permit all of the taxonomic advantages of genera and species The numerous synonyms *culex* and *anopheles* are cases in point.

While holding an open mind in regard to the eventual specific status of *abortus* and *suis*, in the present state of our knowledge it is more conservative, not only from the bacteriological and medical viewpoints, but also from the standpoint of formal nomenclature, to retain the three units as varieties rather than species."

called caprine, porcine and bovine strains possess unique characteristics, it might be well to refer to all of the organisms as "the *Brucella*", and to designate the disease produced by these organisms in animals and man as *Brucelliasis*. The names which have been used to designate the disease in animals and man (contagious or infectious abortion, Malta fever, undulant fever) appear to be inadequate in the light of present knowledge.

*Sources of Infection*

Undulant fever of goat origin is of importance in a relatively restricted area in this country, notably in Texas, Arizona and New Mexico. It is the enormous number of cases of undulant fever due to infection with the organism of contagious abortion of cattle and hogs that has arrested the attention of investigators in this country. No uniformly reliable method for distinguishing between the porcine and bovine strains has been devised.*

*In a recent communication with the author, Charles M. Carpenter makes the following statements:

"Although there are many statements in the literature concerning the differentiation of porcine strains of *Br. abortus* from the bovine strains, I am certain that none of them can be relied upon. For instance, the following conclusions may be found: Theobald Smith stated that the porcine strains produce abscesses in the lymph nodes and spleen of guinea pigs, while the bovine strains do not. In a recent article by Smith on a study of a porcine strain, he concludes that it is more like the bovine strain than any of the others he has examined. McAlpine and Slanetz, in studying the biological activities of this group, concluded that the porcine strains utilize glucose and are more like *melitensis* than are the bovine strains. Soule, by studying the metabolic activities of the two organisms, find that both the bovine and porcine strains utilize glucose. Miss Coleman has just reported a study of the effect of strains of *Br. abortus* on monosaccharids, andd finds that the porcine strains do not ferment these carbohydrates, while the bovine strains do. She has used a different technique from that of any of the other investigators mentioned. Huddleson has reported that the growth of the porcine strains is inhibited by a one to two hundred fifty thousand dilution of gentian violet, while the bovine strains are affected only by one to fifty thousand and one to one hundred thousand. He finds that the bovine strains are more like *melitensis*. Although we have studied only a comparatively few porcine cultures of *Br. abortus* in this country, they do seem to be more pathogenic for guinea pigs than are the majority of the bovine cultures. My opinions are expressed in a discussion at the end of the article by Carpenter and Baker in the Cornell Veterinarian for April, 1927. I do not believe that we are justified in stating that porcine strains have been recovered from cow's milk until we have a more satisfactory method of differentiating these strains. I believe that any strains isolated from cattle should be called bovine, and any cultures from swine should be called porcine, etc. I think that it is very confusing to say that bovine cultures are isolated from man, and that porcine may be isolated from a horse or a cow, etc."

Alice C. Evans commented as follows in a recent communication with the author:

"It is true that the porcine type of *Brucella* infects cattle, and that is also true of the caprine type of the organism. The porcine and bovine types are indistinguishable by the agglutination absorption test, and by other tests. There are, however, certain differences. The porcine type is more pathogenic than the bovine type (see Huddleson's recent article in the October, 1929, Journal of Infectious Diseases). This difference in pathogenicity is one of degree, however, and as both types vary in degrees of pathogenicity, *there is no definite dividing line to distinguish them in this respect.* The bovine type is favored by a reduced oxygen tension in the first few generations after isolation — a distinguishing characteristic which is soon lost. The work of McAlpine and of Huddleson have shown that the two types differ in the fermentation of glucose, and in susceptibility to dyes."

There is some evidence that certain porcine strains are more pathogenic for experimental animals than the bovine variety, but many of the strains which have been designated as porcine have been recovered from cow's milk. Carpenter[4], King[6] and Huddleson[5] have found that the bovine strain has been responsible for the great majority of the cases of undulant fever which they have investigated. Carpenter and King analysed 155 cases of undulant fever and found that only 7 per cent had had any possible contact with swine; no information was obtained in 22 per cent of cases, while 70 per cent were consumers of raw milk, which in the majority of cases was proved to be infected with the bovine strain of *Brucella abortus*. In the 90 cases studied by the writer, there is no evidence of direct goat or hog origin. All of our patients were consumers of raw milk or unpasteurized dairy products. Four cultures of *Brucella abortus* recovered by the writer (3 from cow's milk, 1 from human blood) were found by Huddleson to be of the bovine type. After a careful review of the indefinite evidence as to the relative pathogenicity of the bovine and porcine strains, Hardy[3] states: "A classification of isolated strains is important, but it seems evident that this will not be a reliable index of the importance of the different varieties as a cause of human disease."

That the great majority of human infections with *Brucella abortus* have been the result of the ingestion of the organisms is well established. As regards the dissemination of the disease among cattle, Fitch[17] states that "the chief, if not the only important channel of infection, is through the digestive tract." Hardy[18] has recently conducted animal experiments which have demonstrated that the skin may be a portal of entry. This mode of infection assumes greatest importance in those persons whose occupations bring them in direct contact with infected fresh animal tissues. It is probable that some cases of undulant fever which have occurred in packing house workers, particularly those who "kill and cut", or in veterinarians and farmers who have handled the products of abortion with bare hands, have originated in this manner.

*Distribution Among Cattle*

"Contagious abortion" is an unfortunate misnomer for the disease of cattle and other domestic animals produced by the genus *Brucella*. If one relied only on a history of abortion, less than half of the *Brucella abortus* infections among cattle would be recognized. The disease frequently affects non-pregnant cows; some infected pregnant cows do not abort; the disease commonly affects bulls; calves possess a relative immunity. The disease is widespread among cattle in this country. Ninety per cent of the herds of Connecticut[19] and 86 per cent of the herds of Pennsylvania[20] are said to be infected. Hirschboeck[21] reports that Fenstermacher has tested 16,319 cattle at the University Farm at St. Paul during the past 6 years, of which 4938 (30 per cent) gave strongly positive serological reactions, while 926 (6 per cent) reacted positively in dilutions below 1:100. Our own inves-

tigations indicate that the disease is widespread in southern Ohio. Serological studies of 103 cattle, including 8 calves and 6 bulls, of 7 herds which supplied milk to 18 of our patients with undulant fever, revealed that 76 of the cows (86 per cent) and all 6 of the bulls were positive reactors. The serums of the 8 calves gave entirely negative results; in this regard, it is noteworthy that veterinarians have observed that the infection rarely, if ever, exists in sexually immature animals, and that the susceptibility of young cattle increases with the development of sexual maturity. Farmers' Bulletin 1536 (1927) of the United States Department of Agriculture states that "calves seem to be wholly immune against abortion bacilli." The organism exhibits a predilection for the mammary glands and endometrium of mature cows. Until these tissues have reached full development they do not appear to offer a suitable nidus for the growth of the organism. It seems probable that the same situation obtains during the preadolescent period in human beings.

A single sample of the milk of ten of the cows supplying milk to Dayton patients with undulant fever was found to contain *Brucella abortus* in large numbers. These organisms were serologically identical with cultures derived from the blood of 7 of our patients suffering from the acute manifestations of undulant fever.

In a high proportion of cows whose serums show the presence of anti*abortus* agglutinins, the organism can be recovered from the milk; some infected cows continue to eliminate the organism throughout their lifetime. Schroeder and Cotton[23] found *Brucella abortus* in the milk of 83.5 per cent of cows whose serum showed specific agglutinins for this organism. Carpenter[24] has isolated *Brucella abortus* from the milk of 66 per cent of a group of cows which had either aborted or had retained placenta at least once during 3 previous gestation periods. Special emphasis should be placed on the fact that Carpenter has recovered the organism from the milk of 3 cows whose serums showed no anti*abortus* agglutinins. King[6] isolated *Brucella abortus* from the milk of 2 cows in which no specific serum agglutinins were present. In the 1928 report of the Committee on Abortion of the American Veterinary Medical Association[22], it was stated that "the clean herd is one in which there are no reactors to the blood test". It also states that "the agglutination test does not disclose animals in the incubative stage of the disease." This fact, together with the evidence that occasional cows that are eliminating *Brucella abortus* in their milk do not give a positive blood reaction, led this committee to state: "In order to avoid the possibility of farmers securing the false impression that cattle which fail to react to the blood test will never abort, the Committee recommends dropping the terms 'abortion-free cows' and 'abortion-free herds' when speaking as well as writing about cattle abortion." King also found that 54 per cent of a high grade herd of 151 cows were infected with *Brucella abortus;* even though the milk of this herd was certified, 29.2 per cent of

the infected cows were eliminating the organism in their milk. Carpenter and King[4] found *Brucella abortus* in 20.4 per cent of samples of raw milk supplied to 67 small towns, 2 small cities and one city of 200,000. Fleischner and Meyer[25], after inoculating guinea pigs with certified milk, conclude that "*Brucella abortus* is, for all practical purposes, always present in the certified milk produced in the San Francisco Bay regions." Peters[26] discovered that 39 per cent of the cows supplying certified milk to Cincinnati, were positive *abortus* reactors; this discovery was followed by the passage of a city ordinance requiring the pasteurization of all milk, including certified milk.

*Clinical Manifestations in Man*

Because undulant fever presents many symptoms and signs common to typhoid fever, malaria, tuberculosis and influenza, it is frequently confused with these diseases. Many physicians have arrived at a tardy diagnosis of undulant fever only after repeated negative Widal reactions, the failure to demonstrate the malarial plasmodium, and the inability to elicit physical signs or roentgenographic evidence of tuberculosis. Less often, the disease has been confused with acute rheumatic fever and subacute bacterial endocarditis.

Many writers have stated that the clinical diagnosis of undulant fever entails great difficulties, and that the first thought of undulant fever usually emanates from the laboratory. Our experience does not justify such a belief. In nearly one-half of the Dayton cases the initial clinical diagnosis has been undulant fever, and the aid of the writer was sought only to confirm the clinical diagnosis. Many of the early cases of undulant fever encountered in Dayton were demonstrated at local medical meetings. As soon as Dayton physicians became aware of the characteristics of the disease, an initial clinical diagnosis of undulant fever was made in the great majority of succeeding cases.

Hardy, Bierring and others have found that the disease occurs predominantly in the male sex. In all probability, some of the infections occurring in farming communities are the result of direct contact with infected animals. This fact has been used by some individuals as an argument against milk-borne infection. Persons who have direct contact with infected cattle and hogs on farms are almost invariably raw milk consumers. Furthermore, the male population of most farms exceeds the female. In the urban studies conducted by Hardy, Farbar and Mathews, Jones, Giordano and the writer, in which contact with livestock is practically absent, the disease occurs with almost equal frequency among men and women. In the Dayton series, the females (49) outnumbered the males (41). Urban's studies likewise demonstrate that males are not more susceptible to the disease than females. The great majority of the Dayton patients with undulant fever were engaged in non-agricultural pursuits; only 14 were farmers or dairyman.

Even though children appear to possess the same relative immunity as calves, we have encountered nine *Brucella abortus* infections in children be-

tween the ages of 6 and 10. Kohlbry[27], of Duluth, has recently reported the disease in a one year old infant. In our experience the disease occurs most frequently during the third and fourth decades of life. In 8 families more than one member was affected.

It is a difficult matter to determine the incubation period with accuracy; it has been found to vary from 5 to 14 days.

The prodome is usually that of any general infection, although in 4 of our cases the disease was initiated with a sharp chill and a rapid elevation of temperature to 103-105° F. Ordinarily, the patient becomes gradually aware of an afternoon or evening rise in temperature, associated with chills, nocturnal perspiration, and marked weakness. These onset symptoms are usually acompanied by headache, and pains in the muscles, joints and extremities.

In most instances, the fever, chills and sweats follow a somewhat characteristic course. The patient usually feels quite well in the morning. As the elevation of temperature develops, usually during the afternoon and evening, the symptoms return. The nocturnal febrile exacerbations occasionally reach great heights (106-107°F.). The average maximum fever in our cases was 103° F. There is often a great disparity between the subjective sense of feverishness and the extent of the fever as registered by the clinical thermometer; in many instances, the patient has neither presented a febrile appearance, nor has he complained of feverishness, but the physician has found, to his great surprise, a fever of 102 to 103° F. As the fever abates, chills and sweats occur. If the defervescence is rapid, the perspiration is more apt to be of a drenching character. In 2 of our cases, the febrile exacerbations, chills, and sweats occurred during the forenoon hours. In 24 cases the chills usually one a day, were of sufficient severity to be regarded as true rigors. In 8 of our patients, who experienced fever and sweats, chills were absent.

The perspiration usually occurs during the early morning hours, and in about one-half of our cases was of a drenching character. To such patients, the sweats are the most impressive feature of the disease, since the sense of weakness is pronounced during and immediately after this experience. Many physicians have noted a peculiar sweetish, fetid odor to the perspiration.

In 60 per cent of our cases the pulse rate has been disproportionately slow during the febrile episodes. In the remaining minority of cases the elevation of fever was paralleled by a proportionate increase in pulse rate. Cardiovascular symptoms are not of importance in most cases. A moderate depression of blood pressure was the usual finding. Moore and Carpenter[28], Scott and Saphir[29] and de La Chapelle[30] have reported cases of subacute vegetative endocarditis associated with *Brucella abortus* bacteremia in the first 2 cases, and with *Brucella melitensis*, variety *melitensis A*, bacteremia in the third case.

Marked restlessness and insomnia usually accompany the nocturnal febrile exacerbations. Delirium occurred in 6 of our cases in which the

fever reached great heights. Ordinarily, the mental state remains clear; the sluggish mentality described as the "typhoidal state" was not observed.

The matutinal remissions or intermissions and the nocturnal exacerbations of fever may last from one week to several months. There is indisputable evidence that the disease may persist for several years. The name "undulant fever" was given to the disease discovered in Malta because of recurring relapses and remissions of fever. Recurring febrile relapses have been the exception rather than the rule in our cases, and in those of Hardy, Bierring, and Sensenich and Giordano. Recurring undulations of fever have appeared in only 11 of our cases. In 89 per cent of cases, the patient has experienced but one febrile period, lasting from one week to several months, and finally reaching the normal level by lysis. The percentage of recurrences may be increased as these cases are studied over a longer period.

Approximately one-fourth of our patients experienced a relatively short and mild illness. Eleven patients remained at their work throughout the febrile period, more because of economic pressure than through choice. In most of these cases an original diagnosis of influenza had been made, which leads the writer to suspect that many of the milder cases of undulant fever have been frequently regarded as cases of influenza.

Anorexia was a complaint in about one-half of our patients. The outstanding feature of the gastrointestinal effects of the disease was constipation, which was present in two-thirds of the cases. Amoss[31] has recently recovered *Brucella* organisms from the stools of 2 patients, one of whom was in the sixteenth month of his infection. There is little or no evidence of man-to-man infection by organisms eliminated in the stools. Nausea, vomiting and diarrhea were absent in our cases. The absence of diarrhea helps to distinguish the disease from typhoid fever, in which disease diarrhea occurs in about 30 per cent of cases (Osler). Meteorism, likewise common in typhoid fever, is rare in undulant fever, having been a source of complaint in but 4 cases. The tongue usually becomes coated with a yellowish fur and many physicians have been impressed by the fetid breath.

Loss of weight was an almost constant feature of the disease. The greatest loss was 62 pounds over a period of 6 weeks. Four patients lost more than 50 pounds. Thirty-four patients lost between 25 and 50 pounds. Forty-two lost less than 25 pounds. Ten patients experienced no appreciable loss in weight.

There is often a remarkable absence of positive physical findings. More than one-half of our patients did not appear to be particularly ill. Practically all presented stigmata of weakness and fatigue. The spleen was palpable in one-third of the cases. In only 4 instances was the splenomegaly marked (3 to 8 cm. below the costal margin). In the remaining cases, the inferior pole of the spleen was palpable on deep inspiration at the level of the

rib margin or just above. The liver was palpable in only 4 instances. Generalized lymphadenopathy was not observed.

In 31 of our cases, tenderness or pain of the joints was noted. In 4 cases, the presence of migrating pain in the larger joints led to an initial diagnosis of acute rheumatic fever. Intermittent hydrarthrosis occurred in one case. The organism has been recovered from aspirated joint fluid. The involvement of the joints is apparently due to a transient periarthritis. No permanent impairment of the joints was observed.

Abdominal pain was a major complaint in 16 of the Dayton cases. Among 125 Iowa cases studied by Hardy, abdominal pain was present in 40 cases; in 10 instances it was the chief complaint, and was a marked feature of the disease in 24 other cases. The abdominal pain is most common early in the course of the disease. In 7 of our cases, the pain was located in the epigastrium; in 4 cases, it occurred in the right upper quadrant, while in 5 instances it was most marked in the right lower quadrant. Appendectomy was performed in 4 cases in which there was sudden development of right lower quadrant pain, accompanied by fever. In one instance, gangrenous appendicitis developed during the third week of illness; this case is reported in detail elsewhere[32]. In the other 3 cases, normal appendices were removed. In the latter cases, the surgeons requested the agglutination test for undulant fever after operation in their effort to determine the cause of the abdominal pain. After the agglutination test was found to be positive, a typical undulant fever history was elicited in each case. In one of our cases, cholecystectomy was contemplated because of the development of sharp upper right quadrant pain associated with fever, chills and sweats. The writer has learned of 12 appendectomies and 2 cholecystectomies which have been performed on patients with undulant fever, in which the pathological examination revealed no evidence of any active inflammatory process in the appendices or gall bladders.

There is convincing evidence that *Brucella abortus* exhibits the same selectivity for the genital tract of human beings as it does in cows and bulls. Painful swelling of the testes was a prominent feature of the disease in 16 of our cases and in 4 of Hardy's cases. Seminal vesiculitis and orchitis are common complications in the bull; there is some evidence that the disease may be transmitted to cows by the seminal route. Orchitis is a common result when guinea pigs are inoculated with the organism. Genito-urinary surgeons found evidence of seminal vesiculitis, prostatitis, epididymitis and orchitis in 3 of the Dayton patients. The history and laboratory findings eliminated gonorrhea from consideration. The serums of the 3 men agglutinated *Brucella abortus* in dilutions from 1:160 to 1:640; the organism was recovered in one case from a draining sinus tract which extended from the globus major of the epididymis through the scrotal wall. All 3 of the men were raw milk consumers. None was in direct contact with infected cattle or hogs.

The causative organism derives its name (*Brucella abortus* or the organism of contagious or infectious abortion) from its known etiologic association with abortion in cattle and other domestic animals. It naturally becomes a matter of paramount importance to determine whether or not the disease may have a similar effect on pregnant women. Several reports have appeared[33] describing cases of human abortion occurring on farms where the cattle were known to be affected with contagious abortion. This circumstantial evidence has been augmented by proof as the result of the isolation of *Brucella abortus* by Carpenter[35] from a human fetus which was aborted at the end of the fourth month of gestation. We have encountered 5 cases in which women who have repeatedly aborted, and who presented no clinical or serological evidence of syphilis, gave serological evidence of *Brucella abortus* infection: the agglutinin titers ranged from 1:80 to 1:320. Four of the five women gave histories of a previous febrile illness, entirely compatible with a clinical diagnosis of undulant fever, at intervals from 3 to 6 years previously. All were raw milk drinkers; none had had direct contact with cattle or hogs. A pure culture of the organism has been isolated from a tubo-ovarian abscess which developed as a late complication in a case of known undulant fever. These findings should be a stimulus for further investigations in cases of human abortion.

A skin eruption occurred in 10 of our cases. The lesions were generalized and took the form of small macules in all but one instance, in which the eruption was maculo-papular. In 3 cases, the lesions were most prominent on the abdomen and simulated the roseola of typhoid fever.

The blood count and differential smear yield important information. A mild degree of secondary anemia is usually present. *Leucocytosis is uncommon,* even when the fever is quite high. Leucopenia (4,000 to 6,000) with lymphocytosis is the rule, having occurred in all but 12 of our cases. In 8 cases, the lymphocytosis exceeded 50 per cent. In only 2 cases did the leucocyte count exceed 10,000; in the remaining 10 cases, the white cell count was within normal limits.

The urinalysis usually reveals the trace of albumin commonly found in febrile diseases. The cerebrospinal fluid of 3 of our patients showed no abnormalities.

The average duration of illness in our experience was approximately 4 months. Five patients were confined to bed for less than one week. In one case, there is convincing evidence of relapses and remissions extending over a period of 8 years. While the disease is rarely fatal, undulant fever is of great economic importance because of the long period of incapacitation in the average case. Many individuals are unable to work, or are capable of performing only part-time duties for many weeks or months after the fever has subsided, because of the weakness which is a constant characteristic of the convalescence. One death occurred in our series. Various writers give the death rate as from 2 to 5 per cent.

There seems to be no doubt that many human beings possess a natural

immunity to *Brucella* infection. There is also strong evidence of a great difference in the degree of virulence of the species *Brucella*. As in many other infectious diseases, the simultaneous exposure of many persons to the same strain of organisms will produce no infection in those who possess natural or acquired immunity, but will produce a mild or severe infection in others depending upon the relative degree of susceptibility. Huddleson and Hallman[36] have demonstrated this difference of virulence of the *Brucella* and the difference of susceptibility to infection in *Macaccus rhesus* monkeys. The failure of certain observers to reproduce the disease in animals and man is explainable on this basis, particularly when the organisms have lost their virulence due to long cultivation in an artificial medium. To quote Evans[37], "It is well recognized that pathogenic bacteria lose their virulence when grown on artificial media and this loss of virulence has been commonly noted in the organism of contagious abortion."

*Diagnosis*

If undulant fever is given consideration in the differential diagnosis of all cases of febrile illness, in which the diagnostic criteria for malaria, typhoid fever, tuberculosis, influenza, rheumatic fever or bacterial endocarditis are not convincing, the disease will be recognized with much greater frequency. This is true in cases of vague, mild febrile disease as well as in those in which the clinical manifestations of undulant fever are more clearly defined. In such cases, it should become an established routine to submit 4 or 5 cc. of the patient's blood, collected exactly as for the Wassermann test, to a laboratory equipped with the proper *abortus* antigen for the agglutination test. Practically all of the state health laboratories are now carrying out this simple test. It is now possible to obtain prepared *abortus* antigen from several manufacturers of biological products.

Anti*abortus* serum agglutinins may appear as early as the fifth day, but in most instances they appear sometime during the second week of illness. It is, therefore, unwise to collect the blood specimen for the agglutination test until a week or ten days after the onset of illness. In 7 of our cases, agglutinins did not appear until the third or fourth week of illness. Consequently, it is wise to submit a second and third specimen at intervals of a week in cases in which the first test has been negative.

The whole blood, without the addition of anticoagulants, or the clear serum should be sent to the laboratory. Dried blood specimens on slides are unsatisfactory for an accurate test.

We have used routinely the method adopted as standard by the Hygienic Laboratory of the United States Public Health Service in our agglutination tests. For the past year, we have used as a control the rapid macroscopic agglutination method of Huddleson[38], with uniformly successful results. Using the Antigen-Huddleson (Mulford), this simple procedure is easily adaptable to office use.

We have observed the pro-agglutinoid zone phenomenon, in which agglutination is absent in the lower di-

lutions, but present in the higher dilutions in 4 instances. It is important, therefore, that the test be carried out in all dilutions to 1:640.

The anti*abortus* agglutinin titer rises to variable heights during the acute manifestations of the disease and tends to fall as the fever abates. In most instances, agglutination in dilutions of 1:160 to 1:1280 will be found during the third or fourth week of illness. In one of our cases, agglutination occurred in all dilutions to 1:20,480 during the fourth week of illness. Agglutinins do not remain permanently in the serum with the same constancy that they do in tularemia. Many will retain the anti*abortus* agglutinins for many months or years, while in other cases they will entirely disappear a few months after recovery.

These observations should induce a measure of caution in the interpretation of positive agglutination in low titer. An individual may be suffering from some other febrile disease at the time of the test, and the simultaneous presence of anti*abortus* agglutinins may represent the residual titer of a previous attack of undulant fever.

Carpenter, Boak and Chapman[34] have submitted evidence which indicates that the presence of *Brucella abortus* agglutinins is the result of actual invasion of the tissues by living organisms; they were unable to demonstrate anti*abortus* agglutinins in the serums of adults who had been drinking pasteurized milk containing such antibodies.

The antigenic properties of certain strains of *Brucella abortus* vary widely. Carpenter and Evans have isolated *Brucella abortus* from the blood of human beings whose serum showed no anti*abortus* agglutinins. Carpenter[35] has found that about 6 per cent of patients from whose blood he has isolated *Brucella abortus* fail to show anti*abortus* agglutinins in their serum. Then, too, some patients in whom the clinical picture of undulant fever is well-defined and from whose blood *Brucella abortus* has been recovered, will show agglutination in titers below 1:80. For practical purposes, most laboratorians have regarded titers of 1:80 or above as diagnostic. Evidence recently accumulated hardly justifies such an arbitrary rule. In patients in whom the clinical manifestations strongly suggest a clinical diagnosis of undulant fever, the absence of agglutinins or the presence of agglutinins in titers of 1:10 to 1:40 should lead to further bacteriological and serological studies. We have found the skin test to be of value in such cases.

The occasional cross-agglutination of the *Brucella* and *Bacterium tularense* should be borne in mind. In an investigation of 70 cases of tularemia, the writer[39] has found 6 instances in which such cross-agglutination occurred. In these cases, the relatively higher titer with the *tularense* antigen and the typical clinical history of tularemia left no doubt as to the proper interpretation of the serological findings. Francis and Evans have suggested that all serums from suspected cases of tularemia or undulant fever should be tested for both anti*abortus* and anti*tularense* agglutinins, unless the clinical history points definitely to a recognized source of infection for

undulant fever or tularemia. If it should develop that the *abortus* and *tularense* titers are the same, or nearly so, agglutinin absorption tests will distinguish between them.

We have observed no cross-agglutination with any organism other than *Bacterium tularense*. Nicolle found no cross-agglutination in patients suffering from a variety of non-*Brucella* diseases, principally typhoid fever, malaria and incipient tuberculosis. Occasionally, non-specific agglutination occurs in low titer in uninactivated serums; the pseudoagglutinins will disappear when the serum is inactivated (56° C. for 30 minutes). In over one-half of our cases, a complete Widal agglutination test has been carried out. The Widal reaction was positive in low titer in only 2 cases—in individuals who had previously been inoculated with the triple typhoid vaccine. In view of the clinical similarity between typhoid fever and undulant fever in occasional cases, it is desirable to make it a routine practice to test for anti*abortus* agglutinins in all negative Widal tests. This practice was instituted in our laboratory two and one-half years ago, with the result that 12 cases of undulant fever have been discovered in this manner.

In routinely testing serums for the presence of both anti*abortus* and anti-*melitensis* agglutinins, we have encountered no essential difference in the agglutinin titers. It is, therefore, quite unnecessary to employ the two antigens routinely.

Besides the agglutination test, there are 3 other procedures which may be employed as a means of confirming a clinical diagnosis of undulant fever, namely, (1) the isolation of the organism from the blood, urine or feces, (2) animal inoculations, and (3) the intradermal test.

### *Cultural Studies*

Fifteen to twenty cc. of blood should be collected for culture at the peak of one of the pyrexial waves, and placed directly in flasks containing 30 cc. of infusion broth, varying the amount of inoculum in each flask from 1 to 3 cc. Subcultures should be made from the fourth to the twentieth day on beef liver infusion agar or glucose agar, incubated in a partial anaerobic chamber containing about 10 per cent carbon dioxid. Small "dew-drop" colonies usually appear on the agar slants in two to four days. After 2 or 3 transfers the organism usually grows well aerobically. Certain strains of the organism, particularly the porcine type, will grow well in the absence of carbon dioxid tension. The likelihood of recovery of the organism from blood cultures is not as great as in some other bacteremias. In one of our cases, the organism was finally recovered from the blood after 6 negative results. In hospitalized patients, it is possible to do daily blood cultures; in such cases, the likelihood of isolation of the *Brucella* is much greater than in patients cared for at home, where complete laboratory studies are rarely carried out. It is significant that we succeeded in recovering the organism from seven of ten patients admitted to the hospital. Urinary specimens for culture should be collected through a sterile catheter. The technique for the recovery of the

organisms from feces has been fully described by Amoss.[31]

The danger of laboratory infection is very great. Five workers in the Hygienic Laboratory of the United States Public Health Service have acquired the infection during the course of their investigations of undulant fever. Huddleson has reported 2 cases of laboratory infection occurring in his co-workers.

*Animal Inoculation*

Guinea pigs may be inoculated intraperitoneally with the patient's blood or saline suspensions of macerated tissues. Specimens of heart's blood of the guinea pig may be withdrawn at intervals in order to test for anti-*abortus* agglutinins. Six to eight weeks should elapse before autopsy. Loss of weight, the presence of enlarged joints, enlarged testes and seminal vesicles, whitish foci of necrosis in the enlarged liver, spleen and lymphonodes should be noted. Cultures should be made from the lungs, liver, spleen, kidneys, testicles and lymphnodes.

*Skin Test*

Because of the fact that there are occasional cases of undulant fever in which repeated agglutination tests are negative, there appears to be need for a more delicate test to supplement the agglutination test. Several recent reports indicate that the intradermal test holds considerable promise as a diagnostic aid in those cases in which blood cultures and agglutination tests are negative. Burnet[40] regards the test as more reliable than the agglutination method. Mitra[41], Bua[42] and Trenti[43] have found that the intradermal injection of saline suspensions of killed *abortus* organisms gives specific cutaneous reactions. King[6] has experienced encouraging results in the application of the intradermal reaction to guinea pigs and monkeys previously infected with *Brucella abortus*. Fleischner, Meyer and Shaw[44] regard the test for cutaneous hypersensitiveness in guinea pigs as highly specific; identical skin reactions were obtained when the disease was produced by either the *abortus* or *melitensis* varieties. Giordano[45] has carried out a controlled study of the value of the test in 25 proved cases of undulant fever, with uniformly successful results. In 28 of the Dayton patients, whose serums agglutinated *Brucella abortus* in titers ranging from 1:40 to 1:2560, strongly positive skin tests were obtained in every instance. Thirty-six patients suffering from a variety of other diseases gave entirely negative results. We have injected intradermally 0.1 cc. of a saline suspension of heat-killed *abortus* organisms, adjusted to the standard used in the preparation of the *abortus* vaccine (2 billion per cc.). In earlier studies we used larger doses of a stronger suspension, adjusted to the silica turbidity standard, but we encountered several severe general and local reactions. A positive test is characterized by the gradual development of an indurated red area at the point of inoculation, within 12 to 36 hours after injection. In some cases, a mild transient ascending lymphangitis develops. In the center of the indurated area a pinhead to match-head size, soft, yellowish granuloma developed in about one-

third of the patients. Smears and cultures from this softened area have revealed no organisms and only an occasional pus cell. The indurated area usually persists for weeks or months. A mild elevation of temperature and a slight accentuation of the symptoms usually follows the injection. In all but 4 cases, the agglutinin titer was found to be increased after the intradermal test. In 7 of our cases we have found strongly positive specific skin reactions in patients in whom a clinical diagnosis of undulant fever had been made, but whose blood serum showed no anti*abortus* agglutinins on repeated examination. Specific vaccine therapy produced as effective a response in these cases as it did in the patients from whom the organism was recovered and whose serum showed anti*abortus* agglutinins in high titer. Similar results were obtained in 4 patients with agglutinin titers of 1:40. In the present state of our knowledge, it would be unwise to utilize the skin test as the only diagnostic method. It should be regarded only as an adjunct to bacteriological and serological studies.

*Treatment*

The most important consideration in the control of undulant fever is prophylaxis. Veterinarians have long been aware of the widespread distribution of *Brucella* infections among cattle and other domestic animals. They have become more acutely conscious of its economic importance since the etiologic relationship of contagious abortion in animals and undulant fever in man has been established. Since the disease is so widespread among cattle, it will require many years of diligent effort to control the infection at its source. It is now generally recognized that contagious abortion is of more frequent occurrence and a source of greater economic loss than bovine tuberculosis. Ward Giltner,[46] Dean of the Division of Veterinary Medicine, Michigan State College, recently stated: "It cannot be said that bovine infectious abortion is under control or that it is being subjected to intelligent and effective attempts at control except in a few isolated herds." While veterinarians and public health workers are striving to check the spread of the infection among animals, there seems to be but one logical method for preventing the transmission of milk-borne infection to human beings, and that is by pasteurization. To quote Dr. John R. Mohler, Chief, Bureau of Animal Industry, United States Department of Agriculture: "Infectious abortion is so widespread and the milk of so many animals is infected that the main dependence for protection against whatever danger there may be from *Bact. abortus* in milk must be placed in pasteurization which if properly done will make the milk safe until the dairymen can eradicate the disease from their herds." Our present knowledge of the widespread distribution of undulant fever adds another convincing argument to the many valid reasons which have developed in the past for the universal pasteurization of milk and other dairy products. Zwick and Wedeman[47] found that *Brucella abortus* was killed in 10 to 15 minutes at 60° C., and in 5 to 10 minutes at 65° C. Park[48] mixed several strains of *Brucella abortus* isolated from cattle and swine with cultures of *Bru-*

*cella melitensis,* and made a milk suspension containing 5,00 million bacteria per cubic centimeter; these organisms were killed when exposed to 140° F. for ten minutes, to 142° for seven minutes and 145° F. for five minutes. Boak and Carpenter[49] found that while 8 strains of *Brucella abortus* of porcine, human and bovine origin, grown in milk, varied in their thermal death point, an exposure of 15 minutes at 140° F. destroyed the human and bovine cultures! the porcine strain, while somewhat more resistant, was destroyed in 20 minutes at 140° F., 15 minutes at 142° F. and 10 minutes at 145° F. It is apparent, therefore, that complete pasteurization (143-145° F. for 3 minutes) will destroy the *Brucella.* The need for strict supervision of the pasteurization process is apparent.

The treatment of the disease in human beings has been essentially directed towards alleviation of the prominent symptoms. Chemotherapeutic measures and specific vaccines and antiserums have been employed in a minority of cases.

Mercurochrome and acriflavine have been used intravenously in a small number of cases. Most of the reports are too meager to warrant conclusions. In about one-half of the cases in which mercurochrome has been employed, the results were regarded as favorable; in the remaining cases it was regarded as of doubtful benefit or useless. Ross and Martin[50] found that mercurochrome had no direct effect *in vitro* upon *Brucella melitensis* and *Brucella abortus* in concentrations which it is possible for these organisms to achieve in the blood stream. The employment of acriflavine has not produced uniform results. In a disease characterized by spontaneous remissions, the therapeutic value of any agent is open to question. Mercurochrome was used in 6 of our cases and acriflavine was tried in 5 cases, without any appreciable effect on the course of the disease. Neoarsphenamin was ineffective in 2 cases.

Many observers [Bassett-Smith,[51] Auricchio, [52] Angle, [53] Helwig,[54] Cumston,[55] De Finis,[56] Giuffre,[57] Khaled[58] and Prausnitz[59]] have reported favorable therapeutic results with specific vaccine therapy. Nicolle and Conseil[60] have found that subcutaneous injections of vaccine will protect human beings against subsequent injection of living organisms. Burnet immunized two monkeys with *Brucella abortus,* one with a living culture, the other with a killed culture; subsequent inoculation with living cultures of *Brucella melitensis* produced no effect.

In 46 of our cases, we have utilized a vaccine made from heat-killed *Brucella abortus,* standardized to 2 billion per cc., with such apparently favorable results that we are now employing it as a routine treatment. The vaccine is given by deep subcutaneous injection. The usual dosage has been one-fourth cc. for 3 injections, followed by one-half cc. for 3 injections, followed by 1 cc. doses—all at 3 day intervals. The first one or two injections have been followed by a mild or moderately severe general reaction in two-thirds of our cases, following which the reactions have diminished in intensity after each succeeding vaccination. In several instances the site of injection remained indurated for

many days; no necrosis or abscesses developed.

Following the first two or three injections, the fever usually approached the normal level and the symptoms abated. As a general rule, those patients who experienced the most marked general reaction had a most rapid favorable response to the vaccine.

In order to determine whether or not the results obtained were entirely due to a foreign protein, typhoid vaccine was used in 8 cases and sterile milk was used in 4 instances. In these cases, there was a much more marked elevation of temperature following the injections, but the subsequent course of the disease was not appreciably altered.

Further investigations of the efficacy of the *abortus* vaccine are in progress. It is hoped that other workers will give the *abortus* vaccine a thorough clinical trial and report their observations. Due caution must be exercised in the evaluation of any therapeutic measure in a disease characterized by natural remissions.

### *Summary and Conclusions*

1. Undulant fever is a common and widespread disease of man. The writer reports herewith the clinicopathologic findings in 90 cases of undulant fever, encountered in and about Dayton, Ohio, during the past 18 months. Approximately 2000 cases of undulant fever have been recorded by state health departments during the past 2 years.

2. The etiologic unity of contagious abortion in cattle and other domestic animals and undulant fever in man has been conclusively demonstrated. The manifestations of *Brucella* infection (*Brucelliasis*) in animals and man show a distinct parallelism.

3. No cases of direct porcine or caprine origin were encountered in the series of cases which forms the subject of this report. Both the porcine and bovine strains of *Brucella abortus* are capable of producing the disease in human beings. No definite dividing line distinguishes the degree of pathogenicity of any of the *Brucella*. Available evidence indicates that the great majority of the cases of undulant fever in this country have been the result of the ingestion of raw milk or unpasteurized dairy products containing some variety of the genus *Brucella*. The skin is probably an occasional portal of entry in those whose occupation (veterinarians, farmers, meat handlers) brings them in direct contact with infected animal tissues.

4. Contagious abortion of cattle is widely prevalent in all parts of this country. The disease exists among non-pregnant cattle and bulls; some pregnant cows with the infection do not abort. Calves appear to possess a relative immunity. *Brucella abortus* has been recovered from the milk of cows whose serum showed no anti-*abortus* agglutinins.

5. In man, undulant fever is frequently confused with typhoid fever, malaria, influenza and tuberculosis; less often it is confused with acute rheumatic fever or subacute bacterial endocarditis. Contrary to the general belief that an original clinical diagnosis of undulant fever is made with great difficulty, several Dayton physicians made an initial clinical diagnosis of this disease in nearly one-half

of our cases. An analysis of the manifestations of the disease in man, based upon a clinical survey of our patients, reveals a more or less characteristic clinical picture.

6. The distribution of the disease among male and females was about equal in our series of cases. Children appear to possess a relative immunity to the disease. Only 15 percent of our patients were engaged in occupations which would bring them in direct or indirect contact with cattle or hogs; all were raw milk consumers.

7. Even though the name "undulant fever" implies recurring febrile remissions and relapses, these were observed in only 11 of our cases. One-fourth of our patients experienced a short, mild illness; such cases are easily confused with influenza.

8. No evidence of man-to-man infection was observed.

9. Joint symptoms were an important feature of the disease in one-third of our cases. The frequent occurrence of abdominal pain has led to mistaken diagnoses of appendicitis or cholecystitis.

10. *Brucella abortus* apparently exhibits the same predilection for the genital tract of human beings as it does in susceptible animals. There is considerable evidence that the disease may produce human abortion. The organism is capable of producing seminal vesiculitis, prostatitis, epididymitis and orchitis in man.

11. Leucopenia with lymphocytosis is a characteristic blood finding.

12. The average duration of illness in our series was approximately four months. Fatal termination is rare, having occurred in but one of our cases.

13. Many human beings appear to possess an immunity to the disease. The degree of virulence of the *Brucella* varies widely.

14. Four methods are available for the confirmation of a clinical diagnosis of undulant fever: 1. agglutination test, 2. blood and urine cultures, 3. animal inoculation, 4. skin test. The simplest method is the agglutination reaction. The rapid agglutination method, using Antigen-Huddleson, is a reliable procedure. No arbitrary serum agglutinin titer can be regarded as diagnostic of the disease. In about five per cent of human beings with undulant fever, no anti*abortus* serum agglutinins are present. Blood cultures should be obtained whenever possible.

15. The skin test gives promise of being a reliable adjunct to the agglutination test.

16. The *abortus* vaccine appears to possess considerable therapeutic value.

17. Complete, carefully supervised, pasteurization of milk and dairy products is the logical means of eliminating milk-borne infection.

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# Psittacosis

## A Clinical and Pathological Report of Three Cases*†

By W. W. G. MACLACHLAN, M.D., *Pittsburgh*, H. H. PERMAR, M.D., *Pittsburgh and* C. A. ROGERS, M.D., *Freeport*

THE opportunity to make some clinical and pathological observations on psittacosis was afforded when a small group of three cases in one family was recognized by one of us in his practice (C.R.). One patient, a woman of 53 years, died and an autopsy was performed. The other two cases, a girl of 22 and a child of 9 both recovered. The fatal case presented the appearance of pneumonia but the recovered cases were typhoidal in character, the older girl being very ill for 28 days while the child showed a very mild infection of about two weeks' duration.

A parrot had been given to the patient who died, as a Christmas gift, on December 23, 1929. It was sick when bought, both the buyer and seller being aware of this fact. It had a bronchial infection and a diarrhea. The parrot died on December 30, 1929. Three members of the family did not become ill, although one of them, a young man of 25, had more to do with the parrot than anyone else in the household, as he fed it, cleaned the cage and finally buried it.

*Clinical History of the Three Cases.*

1. Female, age 53, became ill January 2, 1930 with a chill, intense headache, vomiting and a feeling of great tiredness. She had been perfectly well the day before. Headache, vomiting and weakness continued, and about the sixth day of the disease, delirium developed. A harsh, dry unproductive cough appeared on the fifth day and was present to the end, increasing in intensity. There was no expectoration. There was no pain in the chest at any time. From the onset the temperature was high, 104-105, the pulse rate relatively slow, 90-100, until the eighth day of the disease when it became rapid, 120-140, and remained so until death. The respirations were 24 until the sixth day and then gradually increased up to 50 in the latter days of the illness, but even to the end there was no cyanosis and no marked abdominal distention. On the eighth day she developed incontinence of bladder and bowels. The physical signs in the lung were practically negative for the first five days, except for a very few

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râles at the right base, but after this signs of consolidation developed and were heard over all the lobes on the right side and at the base of the left lower lobe. Many râles developed on the ninth and tenth day. The spleen was never palpable. The white blood count was 6,200. A pleural rub was never found. The patient died on January 12, 1930 on the tenth day of the disease.

2. Female, age 22, complained of severe headache and tiredness with nausea and vomiting. Illness began January 4, 1930. At onset the temperature was 104.2, pulse 90, respirations 26. Vomiting persisted throughout her twenty-eight days of illness. The temperature and pulse rate for four weeks, except the last two days, was about the same as at the onset. The fever fell to normal almost as quickly as in a crisis. There was no palpable spleen, no rash, and no pain in the chest suggesting pleurisy. A harsh, for the most part dry, hacking cough developed about the fifth day and persisted to the end. No cyanosis was present. Some white, slightly purulent sputum was occasionally noticed. On the eighth day there was a suggestion of consolidation at the apex of the right lower lobe, (voice sounds increased over the small area and a very few râles). At no other time were the signs more evident, although a few scattered râles could be heard after coughing over both lower lobes of the lung during the second and third week. Patient was delirious for almost the last two weeks of her illness and had incontinence of bladder and bowels during this period. There was no diarrhea. The blood counts during the illness were as follows.

Jan. 12, 1930. Hemoglobin 86 per cent, red blood cells 4,300,000, white blood cells 5,400, polymorphonuclears 69 per cent, large lymphocytes 7 per cent and small lymphocytes 25 per cent.

Jan. 18, 1930. Hemoglobin 89 per cent, red blood cells 4,360,000, white blood cells 5,600, polymorphonuclears 81 per cent, large lymphocytes 10 per cent and small lymphocytes 15 per cent.

Jan. 29, 1930. Hemoglobin 65 per cent, red blood cells 3,840,000, white blood cells 5,600, polymorphonuclears 78 per cent, large lymphocytes 7 per cent and small lymphocytes 15 per cent.

A trace of albumin was present in the urine. Blood cultures on three occasions were negative. The blood serum on the twenty-second and on the twenty-eighth day of the disease showed a negative agglutination test with the B. typhosus, B. paratyphosus and B. aertrycke. On the twenty-second day a B. acidi lactici was was isolated from a specimen of sputum and this organism was agglutinated on two occasions by the patient's serum in 1-160 dilution. Dr. George Lacy who kindly did this part of the work for us regarded this observation as a non-specific one and of no significance. The patient was febrile for twenty-eight days but made a quick and uneventful convalescence.

3. Female, age 9, was taken ill on January 12, 1930 with headache and tiredness. She was sick for about two weeks, but was very mildly ill compared with the previous cases. Temperature for a few days was between 103-104 but gradually fell to a normal level in the course of a week. Pulse and respirations were always

within normal limits. She had very little if any cough, nor any abnormal physicial signs in the lungs. There was no diarrhea nor any vomiting. The symptoms of headache and tiredness lasted a little over a week. The spleen was much enlarged and was palpable for three weeks after the onset of her illness. This was the one outstanding physical sign. The blood counts were as follows.

Jan. 16, 1930. Hemoglobin 75 per cent, red blood cells 3,640,000, white blood cells 4,600, polymorphonuclears 62 per cent, large lymphocytes 7 per cent, and small lymphocytes 31 per cent.

Jan. 29, 1930. Hemoglobin 70 per cent, red blood cells 4,160,000, white blood cells 9,400, polymorphonuclears 41 per cent, large lymphocytes 7 per cent, small lymphocytes 49 per cent, eosinophiles 2 per cent and basophiles 1 per cent.

The urine was normal. A blood culture was negative. Blood serum agglutination was negative for B. typhosus, B. paratyphosus and B. aertrycke. Her blood serum also agglutinated the B. acidi lactici which was isolated from the sputum of Case 2 in 1-160 dilution, but this was not regarded by Dr. Lacy as a significant finding. She made a good recovery.

AUTOPSY OF CASE I.

The body was embalmed. It was that of a large, well developed and well nourished woman. There was nothing noteworthy in the general appearance. The right pleural sac showed many dense fibrous adhesions which were broken down with some difficulty. There was no fibrin on the surface of the lung and no fluid in the pleural cavity. The left side of the thorax was quite clear. The pericardial sac was small and free from fluid. The peritoneal cavity showed no fluid, but a very fatty mesentery, containing small mesenteric lymph nodes. The spleen could not be seen. The edge of the liver was apparent just below the costal margin. No edema of extremities was present.

*Right Lung*: The whole of the lung had a dark red color and the greater part of the lower lobe, the anterior portion of the middle lobe along the superior border, and the upper part of the upper lobe were firm and definitely consolidated. Air-containing lung substance was present between these solid portions. On section, the cut surface was a deep red color, except in the upper lobe where a more grayish appearance was noted. The lung was not a wet lung in the embalmed state. The air-containing substance lying between the consolidated patches was dark in color, due to congestion and anthracosis. The lining of the bronchi was not remarkable. The P. B. lymph nodes were negative.

*Left Lung*: The base of the left lower lobe was firm and on section showed a dull red consolidated area. The rest of the lung was air-containing, and of a dark slate color, due to anthracosis. The consolidation in the left lung occupied only about one-fourth of the lower lobe. The P. B. lymph and bronchi were normal in the gross. The lung was dry.

*Hearts* The heart was small and its chambers were contracted. The valves appeared quite normal, as did also the heart muscle.

*Aorta*: The aorta showed some intimal thickening about the intercostals, but was very clear otherwise, save that there was a little fatty intimal change.

*Stomach and Intestines*: The stomach and intestines were quite normal. There was a pale lining to the whole of the small bowel, and no evidence of hyperplasia of the Peyer's patches or solitary follicles was seen. The mesenteric lymph nodes were not enlarged.

*Liver*: The organ was of normal size and appearance. On section, the cut surface was a little pale, but the substance appeared to be normal. There was no change noted in the gall bladder wall, although the organ contained one smooth, pale cholesterin stone.

*Spleen*: The spleen was quite double the normal size. It was of a deep purple red color and the cut surface was smooth and

dull red with very indistinct Malpighian bodies showing against the red pulp. The tissue of the spleen was firm, undoubtedly due to the embalming.

*Kidneys*: The kidneys were somewhat contracted, showing a roughened, irregular, granular cortex with geographical scarrings when the capsule was stripped. The peripelvic tissue was fatty and slightly increased in amount. On section, the cortex was narrowed. Pelvis of kidney was normal.

*Pelvic Organs*: There were some pelvic adhesions, but the uterus and adnexa appeared to be normal.

ANATOMICAL DIAGNOSIS.
PSITTACOSIS
BRONCHO-PNEUMONIA, (Bilateral)
OLD PLEURAL ADHESIONS, RIGHT.
ACUTE TOXIC SPLENITIS WITH ENLARGEMENT.
SUPERFICIAL FATTY STREAKINGS OF AORTIC INTIMA.
CHOLELITHIASIS.
CHRONIC NEPHRITIS (A. S.)
PELVIC ADHESIONS, SLIGHT.

MICROSCOPICAL

*Lungs*: Sections of the lungs showed an acute inflammatory reaction in various stages of development. The earliest stage was an inflammation of the bronchioles, with an exudate of polymorphonuclear leucocytes and endothelial cells (phagocytic mononuclear leucocytes), mingled with granular precipitate. The epithelial linings of the bronchioles remained intact. The vessels of the bronchiolar walls and of the adjoining alveoli were engorged. The lymphatics showed some dilatation, but contained only granular precipitate with no cellular exudate.

Large areas of the lung were in a state of partial collapse. Here also the bronchioles were filled with acute cellular exudate. The deflated alveoli had unusually thick walls, due partly to engorgement of their capillaries, and partly to a remarkable prominence of the respiratory epithelium. This reaction was the most striking single finding in the lung. The epithelial cells were much enlarged and protruded into the air spaces. Mitotic figures were commonly found in them. The alveolar exudate consisted chiefly of large mononculear cells, (endothelial leucocytes), many of which were phagocytic for carbon or cell debris. Occasionally an irregular, slightly flattened large epithelial cell was found in the free exudate. These were not phagocytic; instead, they showed evidences of disintegration. The epithelial cells were identified by their location on the alveolar wall, the greater size of the cell, the larger and more vesicular nucleus and larger nucleolus, as well as the absence of phagocytosis. The use of a Romanowsky stain, (McNeal), on the tissues showed a light blue cytoplasm in the epithelial cells, and a denser pink cytoplasm in the phagocytic mononuclear cells of the exudate. A few polymorphonuclear leucocytes and moderate numbers of red bood cells were mingled with the exudate. Various quantities of granular precipitate were found. There was no evidence of interstitial inflammation, though the lymphatics were dilated by edema fluid. The pleura showed no reaction where it overlay the lung in this state.

The most acute inflammation was characterized by the elements described, with the addition of various amounts of fine, thready fibrin, moderate numbers of polymorphonuclear leucocytes and a considerable amount of granular precipitate. The enlargement of the alveolar epithelium, with mitosis in many of the epithelial cells, was just as evident here as it was in the partly collapsed areas. Here again, interstitial inflammation was lacking, save for widening of the lymphatics by edema fluid. However, in one section a small vein showed recent thrombosis and a few polymorphonuclear leucocytes in its wall. The bronchioles showed acute exudate. The pleura was not involved, though the most active inflammatory reaction was present in the lung immediately under the pleura.

*Heart*: The sections showed fragmentation and vacuolation of the heart muscle fibers. Their nuclei were palely stained, or sometimes pyknotic.

*Liver*: The sections showed, as in the heart, the cellular changes of acute toxic

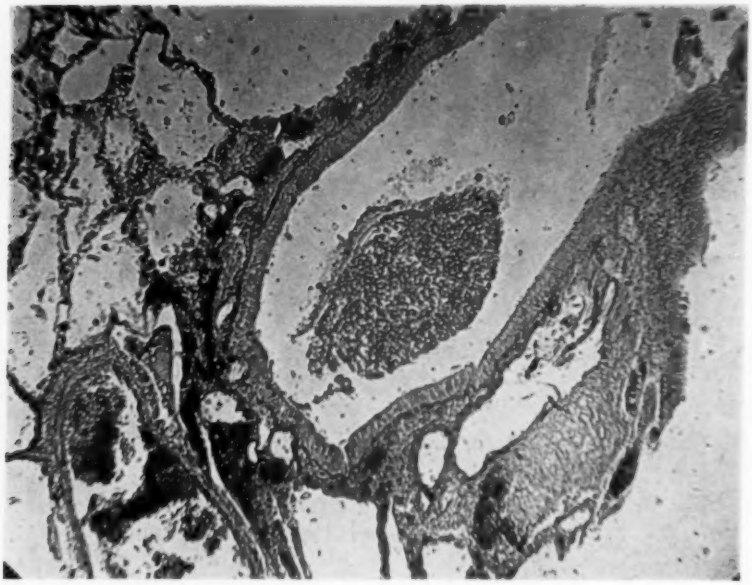

FIG. 1. Bronchiole shows a plug of exudate, and surrounding alveoli are clear. Some engorgement of vessels and dilation of lymphatics. Low power.

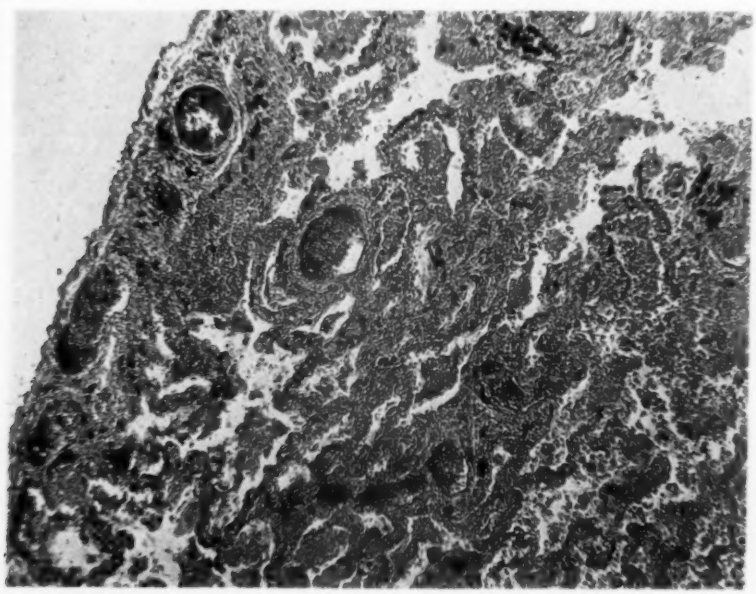

FIG. 2. Lung shows collapse with congestion of vessels, thickening of alveolar walls, and pleura not involved. Low power.

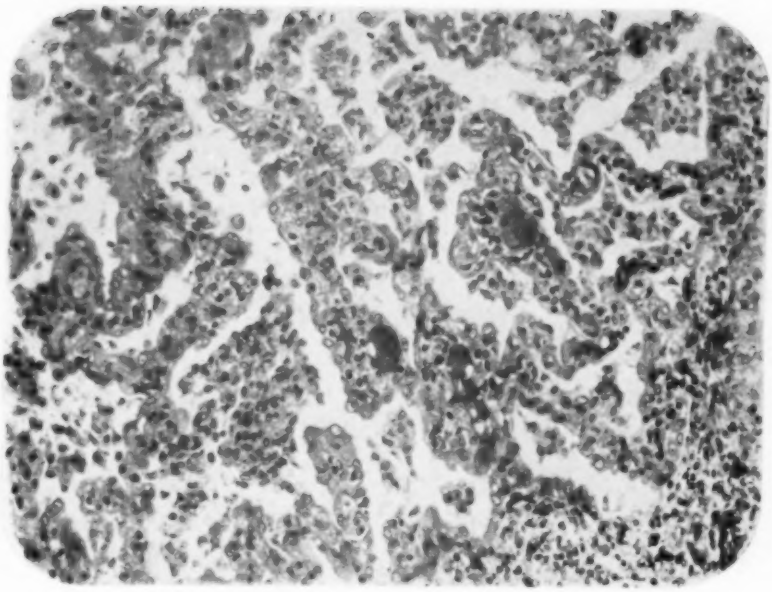

FIG. 3. Higher magnification of the collapse of lung shows widening of alveolar walls with congestion of capillaries, prominent alveolar epithelium and mononuclear exudate in alveoli.

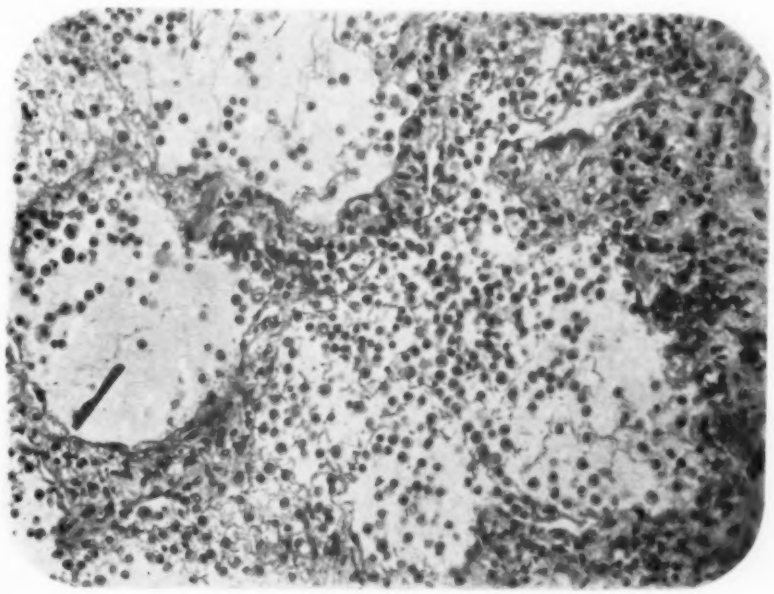

FIG. 4. Lung shows a more acute exudate with polymorphonuclear leucocytes, fibrin and granular precipitate, in addition to mononuclear phagocytic cells. Low power.

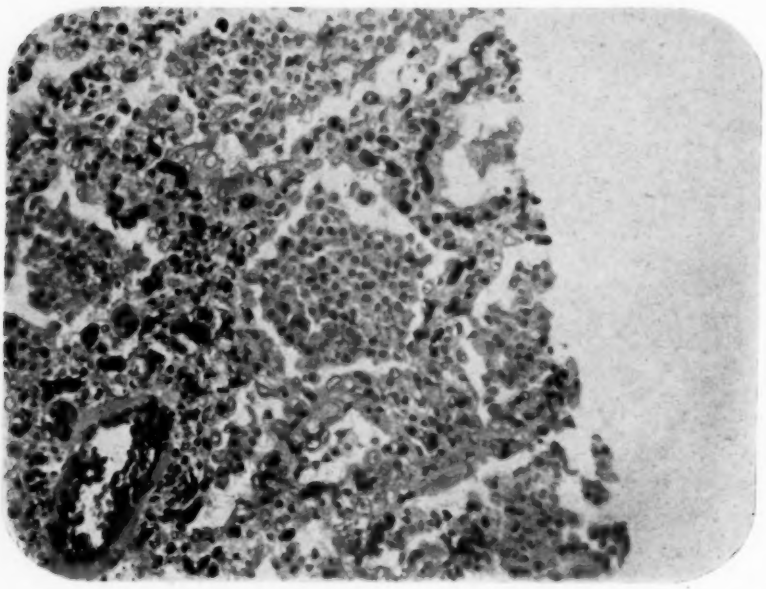

FIG. 5. Lung shows moderate collapse with thickened alveolar walls, capillary congestion and mononuclear exudate. No interstitial inflammation is present. Low power.

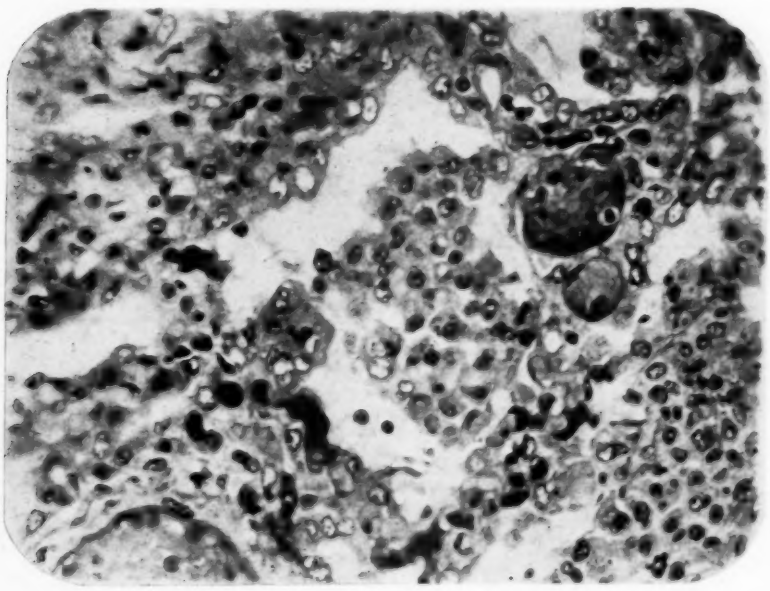

FIG. 6

FIGS. 6, 7, 8. High power of lung shows the prominent epithelial lining of alveoli and the mononuclear exudate.

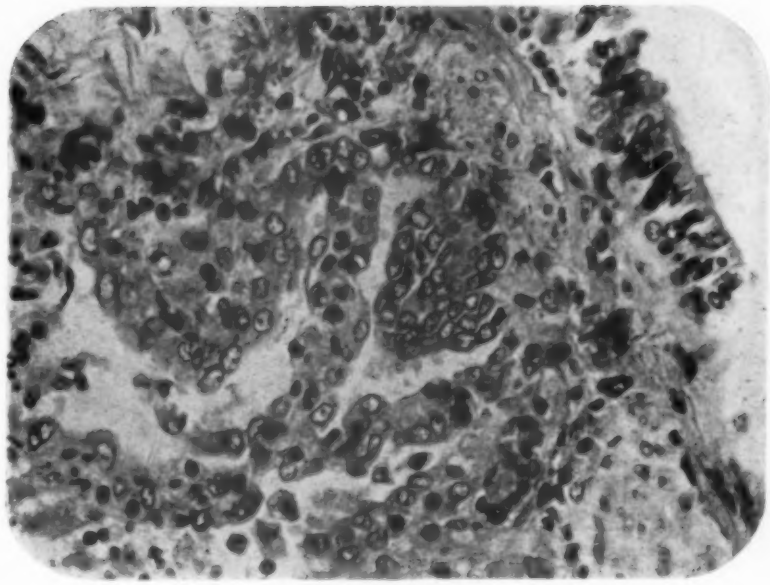

FIG. 7

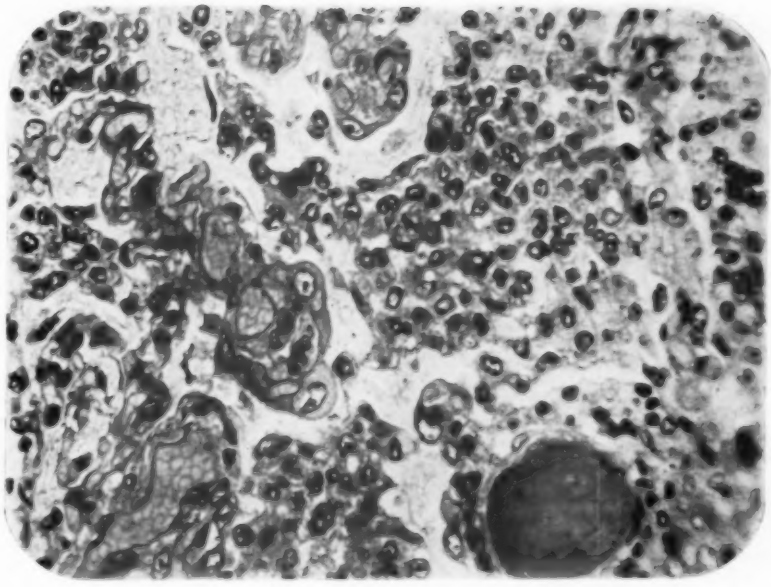

FIG. 8

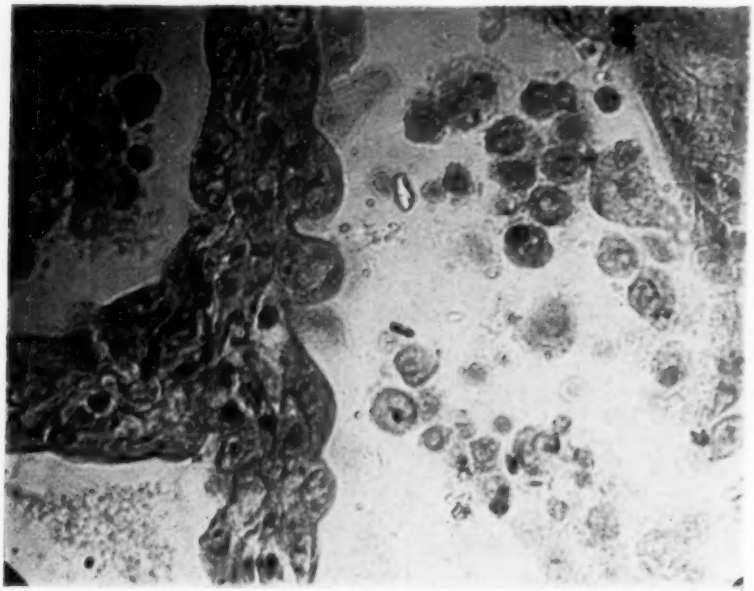

FIG. 9. High power of lung shows the very prominent epithelial lining cells of alveoli.

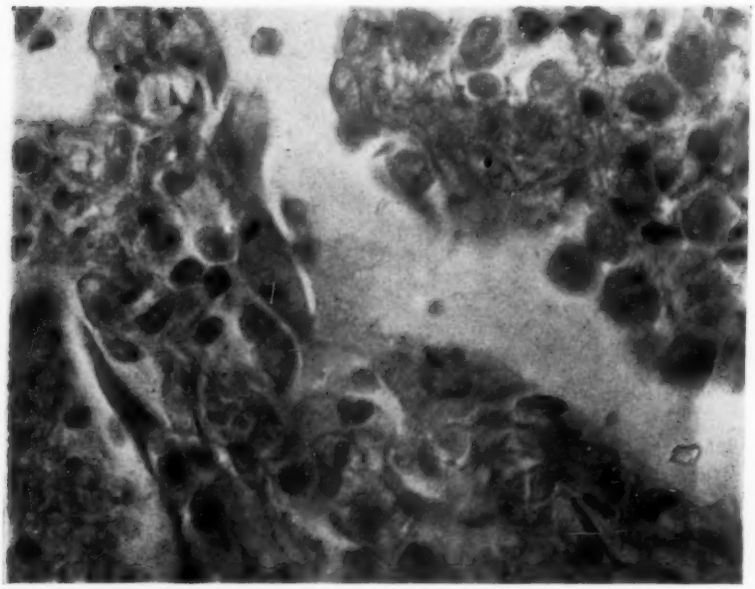

FIG. 10. Nuclear division is seen in two epithelial cells of the lining of an alveolus. High power.

degeneration. The von Kupffer cells were slightly more prominent than usual.

*Spleen*: The outstanding finding in the spleen was extreme engorgement of the sinuses of the pulp. There was no evident increase in free mononuculear cells in the spleen. The endothelial cells lining the sinuses were prominent.

*Kidney*: The sections of the kidney, like those of the heart and liver, showed well marked toxic degenerative changes. In the cells of the convoluted tubules of the cortex were found cloudy swelling, with pyknosis and karyorrhexis in the nuclei.

In résumé, the pulmonary inflammation may be termed a mononuclear broncho-pneumonia, and the outstanding peculiarity of the reaction is the unusual hypertrophy and hyperplasia of the respiratory epithelium throughout the involved lung. The bronchioles show acute inflammatory exudate. Partial collapse of the lung tissue is evident, while interstitial inflammation and extension to the pleura are lacking. The changes in other organs are essentially those associated with an acute infection and its accompanying toxaemia.

The first reference to the disease parrot fever, (Morange in the Paris epidemic of 1894 gave the name Psittacosis from the Greek word ψιττδκσς, a parrot), dates from 1879 when Ritter, in Switzerland, described a group of 7 cases. Three of this number died and autopsies were done by Eberth. The clinical description of the cases that Ritter reported is quite similar to what was later noted by others and also to the reports of the present epidemic. He believed that the human was infected by some unknown germ which was transmitted by the parrot or other tropical birds. He noted the pneumonic and typhoidal-like clinical courses of the disease and he emphasized the fact that the pneumonia clinically was not the usual type of pneumonic infection. The pathology of the lung is not reported in great detail by Eberth but he does refer to one finding in the microscopic study, namely, the presence of many desquamated lining alveolar cells in the exudate of the pneumonia. At that time, however, it is likely true that all mononuclear cells in lung exudate were considered as being of epithelial origin from the lining cells of the alveoli; but one can say that the original paper of Ritter gave a very accurate clinical picture of the disease and also mentioned, although briefly, what we regard as one of the important microscopic features of the lung lesion. In 1892 to 1896, many cases of the disease were reported in Paris and a number of papers written on this subject. According to Desjardin-Beaumetz, who at first considered that the disease was la grippe, upwards of 70 cases with a little over 30 per cent mortality were recorded. The epidemic followed the importation of South American parrots. Nocard, in 1893, described a gram negative bacillus which he called the B. psittacosis. It was isolated from the marrow of the bones of wings which had been saved from birds having died of the disease during the previous year. During the same epidemic Morange, Gaston and Netter found pneumococci and Friedlander's bacillus in the lungs of human cases dying with psittacosis. In 1896, Gilbert and Fournier confirmed Nocard's work, finding the B. psittacosis in the parrot and also in the heart's blood of a patient

dying from psittacosis. They believed the bacillus psittacosis of Nocard was of the paracolon or paratyphoid family. The most detailed early pathological report is by Melenchini who studied a group of cases in 1895 in Florence, following an importation of South American parrots from Genoa with subsequent development of the disease. There is no doubt from his description of the pneumonia, both in the gross and microscopically, that the lesion in the lung was the same as subsequent observers have noted. He refers in detail to the presence of desquamated lining alveolar cells, the small amount of fibrin, the absence of acute pleurisy as a rule and the different picture of this disease from that of ordinary pneumonia. Melenchini frankly doubted the specific nature of Nocard's bacillus. He found pneumococci in the lungs of his cases, but was not certain whether they were the primary infecting agents or merely secondary invaders. He believed that the parrot probably harboured the infecting organism which was transmitted to man, although he put a question mark after psittacosis on the title of his paper. In this country psittacosis was first recognized by Vickery and Richardson in 1904, three cases occurring in New Hampshire. All of them recovered. An epidemic of 26 cases with 5 deaths in Zulpich, Germany, 1909, was reported by Bachem, Selter and Finkler. The clinical feature of most of these cases was a severe pneumonia which at times was peculiar in that its signs were delayed in their appearance and often out of proportion to the great toxicity of the disease. Very little cough was noted and sputum, as a rule, was absent. Weakness, headache, delirium and not much splenic enlargement were noteworthy characteristics. Some cases suggested typhoid. All serological agglutinations were negative. Autopsies showed a pneumonia which Finkler regarded as of streptococcus etiology, as this organism was found in the lungs in the two cases examined. Many mononuclear cells regarded as being of epithelial origin were observed in the alveolar exudate, some polymorphonuclear leucocytes, red blood cells and a little fibrin. The pneumonia was bronchial in type. There was some interstitial inflammation in the lung. These observers did not find the Nocard bacillus and did not believe that it had anything to do with this disease; but, at the same time, they were certain that the etiological agent was a streptcoccus transmitted from the parrot. Warthin, in 1917, in a review of psittacosis stated that the etiological factor of the infection was unknown. In 1920, Perry made a bacteriological study of an organism isolated from a sick parrot, (no human case had been infected by this parrot), and found that it was of the salmonella group, of the mutton type of B. aertrycke. He further stated that the Nocard bacillus which he received from France was the same as this organism by all agglutination tests. He concluded that the B. psittacosis was of the B. aertrycke group. In 1924, Gulland reported the first clinical cases of psittacosis in England. He had two, one being fatal. Beddoes, however, in 1914, referred to the presence of two cases which he had seen in Eng-

land as far back as 1892 but which had never been reported. Thompson in 1929, described four cases, two being fatal. There were no autopsies. In the same year Sailer reported a non-fatal case in this country.

Published studies on the recent epidemic at the time of writing have appeared only in the English and German literature. The present infection appears to have had its origin in the city of Cordoba in the Argentine Republic in July and August 1929. According to Barros, bird dealers congregate there at that time of year to sell parrots which are imported from Brazil and Paraguay. Last year there were many sick birds and subsequently an epidemic broke out amongst the people in Cordoba. The dealers moved to another city, Tucumen, where human cases again developed. Several other towns were similarly infected when the dealers and their parrots appeared. There were probably one hundred cases. The main features of this disease in the Argentine, according to Barros, were as follows: headache, tiredness, rapidly rising fever, vomiting, delirium, intense thirst, relatively slow pulse, no splenic enlargement and variable forms of pneumonia with spasmodic cough but no sputum. In a recent report, (January 1930), Thompson stated that he has records of the existence of 17 more cases, most of whom he has seen. He referred to the sudden onset of the illness, the intense headache, vomiting, diarrhea at times, with marked pulmonary signs later. In some of his cases, on account of the disappearance of breath sounds fluid was suspected but could never be demonstrated by needling. Thompson believed, therefore, that there was some obstructive lesion of the bronchi, and referred to the autopsy on one of his cases which confirmed this finding. This observation is interesting in view of the evidence of collapse of lung that we have noted in our sections. The absence of pain in the chest and of sputum are noteworthy. A pleural rub was found only once. Thompson remarked that the presence of the parrot in the history is still essential in the diagnosis. Wilson, who performed the autopsy on Thompson's case, spoke of the exudate as being almost entirely mononuclear. There was no perivascular or peribronchial distribution of inflammatory cells, (no interstitial inflammatory reaction), small bronchi were filled with desquamated epithelium while the larger were clear. Thompson has informed us that the lesion in the lungs, as shown by some of our slides, which Wilson and he have seen, is identical with their own. In one of Thompson's cases in his first report in 1929 a paratyphoid organism was found in a parotid abscess, and in three of his recent cases, from the cages in which the sick parrots had been kept, Lewis has isolated an organism of the salmonella group. Thompson, therefore, believed it inadvisable at present to rule out entirely the possibility of this form of infection. In a discussion of this paper, Hutchinson referred to 22 cases in London, in which there were 2 deaths. One case seemed to have been a human contact, in that the patients both used the same handkerchief. Horder and Gow have described 9

cases. Some of them were not very intimately associated with the parrot and some not at all, but with people who had been in contact with the birds. Areas of necrosis were seen in the lungs of Horder and Gow's cases at autopsy, but the authors refer to nothing particular in the exudate, although they speak of shed alveolar epithelium bordering plugs of coagulate material in some alveoli. Epistaxis and diarrhea were clinical features of their cases. Bedson, Western and Simpson have made bacteriological studies and are the first, as far as we have been able to find, who present evidence to show that psittacosis is a virus disease. They have been unable to isolate any of the salmonella group from cases of this epidemic. In their observation on parrots it is of interest to note that in one parrot a B. aertrycke was found but this bird showed lesions in the gross quite different from those having psittacosis, and the organism was isolated with the greatest ease from many sources in the dead animal. The blood from six human cases, serum and pleural exudate from two human cases, and filtrates from organs of parrots dying from psittacosis after infecting human cases have produced the diseases in budgerigars; and as the injected materials were otherwise sterile, the authors concluded that psittacosis is a virus disease. They referred to the carrier state in parrots, since it seemed clear that in one instance, 14 months after the parrot had been ill, it infected a human case whose blood subsequently produced the disease in budgerigars. The possible importance of this observation is obvious. Radford has reported 5 cases and Warrack one with very definite histories of contact with parrots. Hegler noted cases in Hamburg in July and in November, 1929. In the first group there were 3 cases, 2 being fatal. Clinically, these cases showed delirium, leucocytosis of 11,000-14,000, with broncho-pneumonia. All agglutination tests were negative. At autopsy the exudate in the bronchopneumonia showed many large desquamated epithelial cells. Some necrotic areas were noted in the lung. The second group were of great interest. A man of 50 died on the 10th day of illness from pneumonia. He had delirium, no cough, no sputum and 4,900 white cells. He had a parrot, but it was not sick. From this patient 5 other cases developed. They were the nurses who attended him in the hospital. All had the same symptoms either of typhoid or pneumonia and 2 of them died, but no autopsies were held. Hegler believed the infection is due to a filterable virus, and that there is evidence of human transmission. Adamy in another report gave 30 cases with 2 deaths in Hamburg during the two epidemics, May and November and December. Fritz Meyer has given an account of 8 cases in Berlin. Three of these showed streptococci in the blood. Weakness, delirium, great thirst, rapid pulse in all save one, pneumonia of a patchy type, no cough, no sputum, no pleurisy, no leucocytosis and a palpable spleen were the clinical features. In two autopsies the findings were interstitial pneumonia, thickened alveolar walls with congested capillaries, very little fibrin, desquamated epithelial

cells in alveoli and enlarged spleen. He believed the streptococcus is a secondary infection and that the disease is due to a virus of the filterable type. All agglutination tests were negative.

The only reference at the time of writing to work done in this country is from the Weekly Bulletin of the City of New York Department of Health, in which it is stated that Krumwiede has shown that the infection is caused by a filterable virus.

*Discussion.*

Psittacosis is a rare disease and even during the periods when it becomes epidemic the incidence of infection is not great. It is certainly not a new malady as it was accurately described in 1879 and, as Meyer has suggested, has recurred approximately every decade since that time, although only two fairly wide spread epidemics have been noted, namely, that of 1892-96 in France and Italy, and the present one. With the more or less constant importation of parrots and other tropical birds over periods of years one wonders why it has not been more prevalent, as the disease is so definite that any large number of cases would hardly fail to be recognized. Seemingly, the infection is not a constant one in the bird. It is also well to remember that tropical birds other than the parrot may transmit the disease and that the African parrot may also carry the infection as shown by Thompson. Undoubtedly, isolated clinical cases in the past have probably not been recognized, although the microscopic picture of the lesion in the lung is so striking that one would imagine that it would have been promptly noted by pathologists if it had occurred to any appreciable extent in cases supposedly dying from broncho-pneumonia. The present epidemic has brought out two interesting features with reference to the transmission of the infection. Bedson, Western and Simpson give a very clear description of one human case infected by a healthy parrot, but apparently a carrier of the disease for 14 months. Also human transmission has been spoken of by Hutchison, and Horder and Gow in England and Hegler in Germany. Studies on the epidemiology will probably throw light on this phase of the subject.

The clinical manifestations of the disease from the first description to the present time have shown in all countries a certain general uniformity. There are, of course, variations as one would note in any disease; even as typical an infection as typhoid fever may show the absence of some symptoms or signs. Psittacosis presents three clinical phases which our cases illustrate very well. Firstly, an atypical pneumonia in symptoms and signs, and highly toxic especially for older people, is the most serious form of the infection. Secondly, a very toxic typhoidal state with variable pneumonic features and persisting for three or four weeks, is seen as a rule in younger adults. Thirdly, a very mild infection from a few days to one or two weeks' duration occurs in young adults and children. This type may appear as an influenza or as a paratyphoid or mild typhoidal infection and could easily be overlooked even in epidemic periods. Age seems

to have some bearing on the manifestations and severity of the disease as Horder and Gow have remarked and as our group, infected from a common source, appears to show. In general the more frequent symptoms and signs are as follows. Sudden onset of a high fever with a relatively slow, pulse, intense headache, vomiting and great fatigue. There is a marked tendency to delirium and in the typhoidal types incontinence of bladder and bowels. In the pneumonic forms are found severe cough, very little or no sputum, no pleurisy nor any pleural pain and a delayed appearance of signs of pneumonia. Usually a low or normal white blood count is noted, although some reports indicate a leucocytosis. Agglutination tests and blood cultures are negative. Three of the Berlin cases reported by Meyer showed streptococcus in the blood, but this is the exception. Certainly, from the clinical point of view one does not have a picture distinct enough to establish a diagnosis of psittacosis without a history of the presence of a sick parrot or other tropical bird.

The discussion on the bacteriology had best be left open until more complete reports are available. It would appear as likely that Nocard's bacillus is going to be replaced by a virus infection as the work of Bedson, Western and Simpson in England and Krumwiede in this country have indicated. Further, this view is also held by the German observers, Meyer and Hegler. Pneumococcus, streptococcus, B. mucosus capsulatus and the salmonella groups are probably secondary invaders. The clinical and pathological picture of the disease may be somewhat influenced by the type of secondary invader.

On account of the fact that psittacosis is a rare infection the opportunity for pathological study of autopsy material has obviously not been great in recent years, although as we have indicated previously in a review of the literature, the lesion in the lung has been described by some early observers in detail in its gross and microscopic picture. It is our belief that the past and present descriptions refer to the same process, although microscopically the interpretation of the mononuclear exudate differs. The older writers believed that these cells were desquamated epithelium from the alveolar linings; our own view, in accord with present opinion, is that they are mononuclear phagocytes, derived from the reticuloendothelial system. In the gross the pneumonia is as a rule of the bronchial type, persisting in a state of red hepatatization even when, from the duration of the disease, a grey hepatatization might be expected. Horder and Gow remarked that the lung had the appearance of an infarct, and it is of interest that thrombosed vessels have occasionally been found. The usual absence of fibrinous pleurisy is noteworthy and explains the freedom from pain. A moderate splenic enlargement with intense engorgement, and absence of any hyperplasia of the lymphoid structures of the bowel and mesentery complete the picture. The gross appearances of the tissues at autopsy are, therefore, not exactly distinctive nor diagnostic. It is further to be kept in mind that the autopsy findings, both gross and microscopic,

in a case dying on the 10th day, as did our case and one dying in the third or fourth week, might present different pathological features.

The inflammatory reaction in the lung may be interpreted as a primary diffuse bronchitis, affecting chiefly the smaller bronchi and bronchioles. The exudate in the air passages causes occlusion of their lumina, after which there is a degree of collapse of the alveoli distal to the occlusion. It would appear, however, that the virus reaches the air cells before the occlusion of the finer air passages, where it gives rise to an inflammatory reaction that is essentially mononuclear, and at the same time causes either a proliferative or a regenerative response on the part of the respiratory epithelium. The considerable number of mitoses present in the enlarged epithelial cells indicates an active process. This reaction is an extremely unusual one in connection with acute inflammations of the lung, and is the only distinctive microscopic change found in this case. The essentially mononuclear character of the exudate suggests a milder, non-destructive type of irritant action, and this point is borne out by the evident stimulation of the epithelial lining of the alveoli. The most intense reaction falls short of that in a typical acute pneumonia. Fibrin in scanty, and mononuclear phagocytes predominate in the exudate. Interstitial pneumonia is practically lacking in the present case, the lymphatics showing only the widening associated with oedema. Only one instance of thrombosis of a small vessel was encountered in many sections from all parts of the lungs. It is quite possible that a secondary infection may explain the fibrino-purulent character of the most active inflammation, and possibly also the fatal termination. Gram-Weigert stains on the tissue showed a few bacterial forms suggestive of pneumococci.

## *CONCLUSIONS.*

1. Three cases of psittacosis are described clinically with autopsy findings in one case.
2. The clinical picture may be one of atypical pneumonia or of a typhiodal state. The mortality occurs in the former, especially in older individuals.
3. The pneumonia is of the bronchial type with collapse of lung and the exudate is chiefly of phagocytic mononuclear cells.
4. The most distinctive feature in the pneumonia is an hypertrophy and hyperplasia of the epithelial cells lining the alveoli. However, these cells do not enter into the formation of the exudate.
5. The most recent work would indicate that psittacosis is caused by a filterable virus.
6. At the present time a diagnosis of psittacosis cannot be made without establishing contact, direct or indirect, with a parrot or other tropical bird.

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NOTE. Since our report was written, some articles on psittacosis have appeared, and as they refer to important phases of the subject we wish to make a very brief reference to them. Hutchison, Rowlands and Simpson, in a study of the London cases, (British Med. Journ., April 5, 1930, 633) have given a detailed description of one case that came to autpsy on the 22nd day of the infection. They noted the hyperplasia of the epithelium lining the lung alveoli and have observed some of these cells in nuclear division. We have regarded this as our most distinctive lesion in the lung pathology, and in view of a similar finding by these authors, it may be, in fact, the most characteristic picture. Capillary thrombosis, which they have seen, is possibly related to the duration of the infection, as this was not noted in our case who died on the 10th day of the disease.

From the U. S. Public Health Service, Armstrong and McCoy (Public Health Reports, April 4, 1930, 45, 725) have demonstrated a filterable virus by experimental methods. Lillie (Public Health Reports, April 11, 1930, 45, 773) has shown Rickettsia-like inclusions in the endothelial cells in the lung, liver and spleen in parrots and in one human case. We have been able to confirm Lillie's findings in an occasional endothelial cell in the exudate and in the alveolar walls of the lung, but we have not seen any of these bodies in the Kupffer cells of the liver or in the endothelial cells of the splenic sinuses. Finally, McCoy (Public Health Reports, April 18, 1930, 45, 843) has given further evidence of the great infectiveness of the virus of psittacosis in showing that 8 out of the 11 cases who developed the disease at the Hygienic laboratory were in no direct contact with the infected birds. The exact mode of infection, according to McCoy, was not known, but it was apparently "through a contaminated environment". He did not appear to regard human to human transmission in his cases as likely.

# A Committee on Applied Medical Science

By James M. Anders, M.D., M.A.C.P.

THE writer feels strongly that fresh discoveries of greater or less importance fail of being utilized in a practical manner as promptly as they should be, so that our scientific achievements have ever outstripped our practical performances in the past. He has in previous articles dwelt upon the fact that popularization of science has been lagging too far behind the march of scientific advances, and urged the need of measures or practical means to facilitate the serious application of important fresh discoveries. As stated elsewhere by the writer; "It is to the utilization for human progress of established truths, in even greater degree than to pure fundamental research, that college and university students should devote themselves."[1]

The research method of study should include the reasonably prompt application of newly discovered facts. It should be the function of the university and college to follow the original achievements of the laboratory with prudent attempts to insure their prompt application as far as possible, for the benefit of mankind. Too often, then, well proven scientific discoveries fail to be translated into human uses until after a long period of delay. For example, when nitrous oxide was first produced it was known, and used only, as "laughing gas", but now, many years later, it is being used extensively by both the dentist and the surgeon as an anesthetic.

Again, ether as an anesthetic was discovered long ago—some 300 years—before it came into common usage to relieve the pains occasioned by surgical procedures. More especially in recent times, during which the discoveries of science have shown a great numerical increase, has the human race failed to receive the benefits of which they are capable, as quickly as has seemed possible and desirable.

The use of diphtheria toxin-antitoxin was first suggested by Dr. Theobold Smith to prevent diphtheria, in 1907, and in 1913 von Behring demonstrated its safety when employed as a prophylactic among young babes against that dreaded disease. It was not, however, until more than ten years later that a serious effort on the part principally of public health officials, was made to immunize children against diphtheria. It is not known definitely what percentage of childhood in the susceptible period has been protected to date, but it is doubtless less than fifty per cent. Who will compute the loss to humanity in lives alone from such unreasonable and unjustifiable delay?

True it is, that during the last three decades there was available diphtheria antitoxin for the treatment of this affection and by this specific means the mortality rate has been kept as low as ten per cent. Moreover, it is to be recollected that if this remedy had been administered early, and in proper dosage in all cases, there would be practically no mortality. It has not seemed possible to accomplish this, however, hence the necessity of administering universally the toxin-antitoxin if we would hope to eradicate this disease. It was confidently predicted a few years since, by certain leading public health workers, that in the course of five years diphtheria would be exterminated in some quarters, at least. And this prediction would have come true, had public opinion been sufficiently aroused, or enthusiastically and universally favorable.

It is a sad commentary that medicine as an art of practice has not kept pace with medicine as a science, for the reason that not all available means of prevention and relief and cure have been employed. That the laity should accept the notable scientific advances with indifference is not to be wondered at, since it is unmindful for the most part of their practical significance. On the other hand, to educate public opinion to a point at which it will co-operate with public health officers in applying scientific knowledge to human uses, has been found to be difficult. Fortunately, many welfare agencies and organizations, as well as the organized medical profession, are at present writing giving intelligent help in this direction, but these do not bestow exclusive attention to the field of preventive medicine.

Many scientific advances outside of the field of medicine have met the same fate. To illustrate, gunpowder was used for amusement by the Chinese centuries before Europeans put it to its present day uses. The Wright brothers learned how to fly by using the airplane as a glider. As pointed out by Slosson, however, "aviation would have remained for a generation or so in the class of amateur sports, but the war forced it pre-maturely into maturity, possibly not to the advantage of its development". Another illustration may be cited; it is known that the steam engine was a mere plaything in ancient Alexandria, but some seventeen hundred years later, Watt converted it into a working machine.

Again, the comforts and conveniences of modern life are to be credited to the physical sciences, including applied science, and these comforts and conveniences unknown to our forebears received more interested attention than do many of the more fundamental laws affecting the health and lives of the masses. A systematic study by any person of average intelligence of the elementry physical sciences will reveal laws and facts long since given to the world, but of which he or she had been in blissful ignorance. He would learn the well-known fact that to live a sane hygienic life he must live in harmony with the laws of nature, and that ignorance of these does not excuse him.

It has been well said that every adult who has never been to school gains a fragmentary knowledge of the physical sciences, but obviously can not

make full use of it. What such a person needs is to acquaint himself with the simple elementary yet well established facts and laws appertaining to the physical sciences and then promptly apply them to his daily life and habits. Even among the cultured classes the fundamental laws of health are frequently overlooked. It is another instance of failure to make proper use of established scientific truths.

It is not always the most important laws, that are first fully applied to daily living. To determine the cause of the frequent delay, however, is a puzzling question. Once a verified, safe preventive for a dreaded infectious disease is found, it would seem that its universal, intelligent use must follow promptly and the disease be eradicated, but such is not the case as has been shown above by convincing data concerning diphtheria. It is true, on the other hand, that the prompt application of specific means of prevention in infectous diseases would confer the greatest benefit upon mankind. Here may be mentioned the fact that while modern medicine has protected the human race against some of the most devastating infections,—for example, smallpox, typhoid fever, cholera, tuberculosis, typhus fever, yellow fever (in America) and others, there has not been the active co-operation on the part of the organized medical profession and intelligent laity in that progress, more especially in the matter of the practical application of the scientific discoveries which made it possible, that could have been desired.

One of the principal purposes of this paper is to direct attention to the importance of promptly putting into effect, more especially, such positive advances as are emanating from the laboratory, and have a bearing upon human health and welfare. Care should obviously be taken to avoid precipitancy, which would compel a too frequent reversal of attitude toward these advances.

The suggestion is advanced here, that a council of experts be appointed by a nationally organized medical body such as the American College of Physicians. Such a council or committee could determine the practical significance of new scientific discoveries in hygiene, medicine and preventive medicine, and could also create an enlightened public sentiment with regard to those calculated to promote human welfare by new, though well established means and methods. It is clear to the writer that such a medical council or committee, if carefully selected, would be powerful in hastening the utilization of useful and life saving measures based on verified laboratory results.

The manner of collecting reliable data and the best method of rendering it understandable to the general public are details of importance, it is true, but cannot be discussed here. Suffice to add that experts such as would most probably be selected to make up the council, already know where this is to be found and its purport. The council, made up of expert clinicians, pathologists and bacteriologists, would be naturally expected to make a report annually to the American College of Physicians, in addition to its work of public illumination and education, and to publish

the results of its deliberations during the intervals between the meetings of the College as occasion might seem to demand. The writer feels that its voice would be welcomed and heeded by the general profession.

Such a body of experts would vigorously attack the problem of diffusion of established knowledge not only regarding the causes and approved methods of preventing the communicable diseases, but also those chronic degenerative affections which are taking an increased toll of human beings; it would stimulate the members of the medical profession to greater personal efforts to educate public opinion,—a step so necessary to progress in disease prevention.

The institution known as Science Service at Washington, and headed by the eminent scientist, Edwin E. Slosson, is doing much to popularize scientific knowledge in this country. It, however, does not stress subjects, hygienic and medical, sufficiently, and to obtain the best results we must go to experts in these well-defined fields, and gain their active organized cooperation in some such way as outlined above. In this manner, and in this manner only, can the many aspects of scientific inquiry, as related to disease and its prevention, be interpreted promptly to the general public and the profession. Steps might be taken by the committee of experts, here suggested, to co-operate with the Science Service above referred to, as well as other agencies, and in this manner the service to humanity be broadened and rendered more effective.

Surely, discoveries that have rendered fatal diseases obedient to our control should be interpreted correctly by the medical profession to the humblest citizen. It seems to me, it is time to overhaul our ideals so that greater efforts will be expended in enlightening the people through the medical profession about the scientific advances which promote human health and happiness, and to a like extent, material progress. To accomplish this objective within a reasonable length of time will prove a difficult undertaking, but since there is urgent need for it, effective ways and means should be found. The method advanced above would provide another opportunity for the organized medical profession of America to extend its influence and increase its usefulness to mankind.

[1]General Magazine and Historical Chronicle, July, 1929, p. 479.

# Healing of Tuberculosis*

By F. M. Pottenger, M. D., *Monrovia, California*

We are able to estimate the value of therapeutic measures as applied to any disease in proportion to our understanding of the manner in which the body naturally combats such disease.

Infectious diseases, as they affect different people, produce a varying picture. While the same disease is always produced by the same microorganism, yet identical conditions whether in pathology, symptomology or in ultimate results will never be found.

Grant that all human beings would react toward a given microorganism in the same general manner, variations in the disease picture would still occur because of the differences in virulence and differences in numbers in the causative microorganisms; on the other hand, grant that dosage and virulence in infectious microorganisms were always the same, they would meet varying conditions of tissue response in different individuals and in the same individual at different times, which would likewise produce disease pictures of great variation.

Applying the above principles to tuberculosis we shall see that the tubercle bacillus acting upon different individuals produces disease pictures of great variety, which are combatted with different degrees of effectiveness.

### *Principles Underlying Healing of Tuberculosis.*

Regardless of variations in the disease and differences in the outcome of tuberculous infections, the body carries out its program of protection along certain definite lines, the nature of which we may inquire into with profit. The defense in tuberculosis seems to be largely cellular, yet we can not deny that a certain amount of humoral defense is likewise brought to bear against the invaders (McCutcheon, Strumia, Mudd and others,[1] and Opie.[2]

The program of defense differs according to whether it is a first or a succeeding infection. The former is opposed at first by only the natural defense of the host, and later by a developing specific defense; the latter by both natural and specific defense from the start.

Inasmuch as the host shows evidence of immunity in from five or six days to two or three weeks after infection has taken place, and since no symptoms appear until the immunity mechanism has been called into

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action, in our study of clinical tuberculosis we are always dealing with infection in the immune; so the specific factors in defense are always present and upon the degree of their competence depends largely the nature, the course, and the outcome of the disease.

Healing in tuberculosis in the immune or adult type, as we speak of it, is accomplished through several different processes, among which are: (1) destruction of bacilli; (2) retardation of the passage of bacilli through the tissues; (3) elimination of bacilli through natural channels by caseation and cavity formation; (4) development of a state of desensitization to bacillary and other toxins. (5) encapsulation or rendering inactive, viable bacilli which remain in the tissues; (6) ridding the body of the inflammatory products which accompany the infection; and, (7) repair of the injury inflicted upon the body by the disease.

In studying tuberculosis as we meet it day by day in the clinic, we get the impression that *healing depends upon the controlling of the size and the effects of the reinoculations and keeping them within the range of the individual's powers to cope with them.* To this end the acquired bactericidal action of immune tissues, the retarding influence of the allergic inflammation upon the passage of bacilli through the tissues, and the desensitization of the host of toxic substances, are probably the major contributing factors. Many otherwise large and dangerous reinoculations are thus rendered ineffective and eventually overcome.

*Destruction of Bacilli.* To what extent destruction of bacilli takes place in the course of healing of a tuberculous process, and how important this factor is in cure has never been satisfactorily established by experiment. Kraus and Hofer[3] reported that they observed destructive effects upon bacilli within an hour after they had been introduced into the peritoneal cavity. Wolff-Eisner[4] speaks of a lytic action upon the bacillus which takes place within the body. Certain humoral effects have been shown by the presence of antibodies in the blood by numerous observers, but most observers have considered them as being of secondary importance, when compared with the cellular response of the host. The action of phagocytes was established by Metschnikoff[5], and Wright[6] showed the effects of opsonins in preparing the bacilli for phagocytosis.

Recently new data bearing upon the subject has been brought forth. Rich[7] believes, although he offers no direct proof, that destruction of bacilli is a very important mechanism granted to the body by a previous infection. Lurie[8] reports experiments in which, by using one type of bacillus for primary inoculation and another type for reinoculation, he has been able to show that the resulting pathogenesis was due to activity on the part of the bacilli remaining in the tissues from the first infection, and that the bacilli of reinoculation were practically all destroyed, without preliminary multiplication.

I have long assumed that an enormous destruction of bacilli must take place in the bodies of patients suffer-

ing from clinical tuberculosis. It has seemed to me to be the only way that we can understand the healing of an extensive lesion. Such visible infections as those in the eye, testicle and larynx are of comparatively frequent occurrence in the course of chronic pulmonary tuberculosis, and very often prove to be abortive showing that the bacilli have been destroyed. Other infections which take place from one part of a lung to another, and prove to be only temporary affairs, are frequently noted when patients with advancing lesions are closely watched and frequently examined, and particularly when frequent x-ray plates are taken for comparison. Often such serial x-ray plates show a new focus to appear in a certain part of the lung field, only to clear away after being present for a brief time, say a month or two. The very fact that bacillemia, which is so often present, fails to cause uncontrollable extensions regularly is further proof of the body's destructive action on bacilli.

*Retardation of Passage of Bacilli Through the Tissues.*

The allergic inflammatory reaction performs what is usually recognized as a special protective service in inhibiting the free passage of bacilli through the tissues. Were it not for this service nothing but a quick and efficient bactericidal action on the part of the body tissues could save any one suffering from advancing tuberculosis from destruction, yet the recovery of such patients is a common observation in clinical practice. Koch[9] first observed the restraining influence of allergy and Krause and Willis [10 11] showed the extent of the retardation experimentally. They showed that bacilli are carried from the site of inoculation to the adjacent lymph glands in nonimmune pigs in an hour; but require two weeks in the immune. They make the circuit of the entire body and are found in the organs generally in three or four days in the nonimmune, but require three or four weeks in the immune. Inasmuch as preventing the disease from spreading is a condition necessary to healing it readily can be seen how important and how necessary this property of allergy becomes to the tuberculous host.[12 13]

In normal hosts, bacilli lying in the air passages are quickly picked up by phagocytes and carried through the alveolar and bronchial walls, as has been shown in experimental animals. In advanced tuberculosis, where not a few bacilli at infrequent intervals, but millions of bacilli daily, are found in the air passages under conditions in which phagocytosis is increased, in order to account for the failure of infection to take place we must assume either that the bactericidal power which exists on the part of the immune tissues of the host have attained almost an unbelievable degree of competency, or that the tissues themselves resist the entrance and transport of the bacilli. Rich[7] does not believe that the evidence for the restraint of bacilli from entering and passing through the tissues is sufficient, but believes the real defense, which has been so generally observed from the early experiments of Koch[9] to the present time is due to the destruction of bacilli

and not to the retardation of their migration in the tissues

Opie,[14 2] on the other hand, has recently reaffirmed his view formerly expressed,[15] to the effect that immune tissues fix foreign protein at the site of injection from which it may be recovered for a period of time, and states that anaphylactic shock is prevented by this local fixation process. While this may not prove that the same thing is true of bacteria, he calls attention to the similarity of behavior of the immune tissues to tuberculin, abortin and other similar bacterial products, and also cites, apparently with approval, the experiments of Cecil and Blake[16] who found that the blood stream of monkeys vaccinated against pneumococci by intratracheal inoculation shows less invasion than the unvaccinated.

*The Elimination of Bacilli from the Body by Necrosis and Cavity Formation.* The elimination of bacilli through the natural channels of the body, such as the bronchi, bowel, and urinary tract becomes an important phase of defense in extensive lesions.

In advanced destructive lesions large numbers of bacilli are gotten rid of daily by being ejected from the body through the bronchi, and countless others through the gastrointestinal canal. During the time that these bacilli are within the natural channels of the body, if the patient were not protected by some specific barrier of defense, he would be in danger of their penetrating into the tissues and forming new foci of disease.

The destruction of tissue as it occurs in pulmonary tuberculosis through the breaking down of conglomerate tubercle and cavity formation with the discharge of the focal contents into the bronchi to be carried outside of the body must be looked upon as having paradoxical interpretation. The destruction is due to the relatively large numbers of bacilli engaged in the reinoculation at a time when the tissues are markedly sensitive to tuberculoprotein. It would not take place if the infection were produced by a few bacilli only, even if sensitization were marked; but it results because of massive dosage when sensitiveness is marked. It is doubtful whether any host could withstand the disease which would be caused by such quantities of bacilli should they scatter into the tissues, if we may judge by the consequences of ruptured bronchial glands and the resulting caseopneumonic lesions which follow, or of miliary infection following severe bacillemia. So from this standpoint the destructive process is without doubt conservative. Nor could the tissues heal with such masses of bacilli within them. Therefore, unless the host is able to destroy the large numbers of bacilli contained in the caseous masses, the only opportunity for healing must come through their expulsion, even though damage be done to the host by the loss of tissue.[17]

*Desensitization of the Patient to Toxins.* While we have no method of measuring the toxins which a patient withstands during the course of pulmonary tuberculosis, it seems reasonable to assume that his capacity to withstand must increase many fold as the disease progresses; for a small limited lesion at the beginning of infection will cause a syndrome of se-

vere toxemia with equal or more prostration than will be caused later when the infection has extended and multiplied many fold and increased the amount of toxins enormously.

It is undoubtedly one of the results of the action of the patient's own tuberculoprotein that it desensitizes him and prepares him to withstand larger and larger doses of bacillary protein without serious harm. This seems to be a necessary part of the immunity mechanism without which patients with advanced tuberculosis would not be able to endure their disease, let alone having an opportunity of overcoming it. (Pottenger[18]) It is also probable that the patient is desensitized to the toxins produced by his own tissues. This is illustrated by the following case:

No. 9564. Mrs. E. W. Aged 35 years. Entered sanatorium May 5, 1929. Important previous history: measles at 32—quite severe; appendectomy at 27; operation for acute ileus at 30; influenza at 35; pneumonia at 31, followed by pleurisy for three weeks. Excellent health except dry hacking cough up until October 1928, when she developed severe cold followed by persistent cough and expectoration. Treated for bronchitis. Another severe cold December 1928. Temperature not taken. Tuberculosis not suspected. During April 1929 patient complained of severe exhaustion; loss of appetite, poor digestion, nausea, eructation of gas, profuse sweats, right-sided pleurisy, a loss of fifteen pounds in weight, and severe cough with considerable sputum.

The temperature and pulse curves for a period of eight months, and X-ray films taken at intervals during the eight months, are shown in Fig. 1 and Fig. 2 A, B, C, and D. On entering the sanatorium patient was too weak to sit up for examination. Showed extensive bilateral tuberculosis; caseopneumonic in type, throughout upper half of the left lung, with cavitation, and a lesser infiltration in the upper third of the right lung, as shown in Fig. 2 A. Temperature 103-104°; pulse 90-108, as seen in chart, Fig. 1. The disease continued to extend and showed increased areas of softening, as indicated in the film Fig. 2 B, taken August 30, 1929, which shows entire left lung involved. Temperature, however, had become lower, as will be noted in the chart. Appetite improved; digestive disturbances lessened; and sweats disappeared. Patient felt much better. This improvement in symptoms continued through November, although temperature remained high, and as will be seen in the film Fig. 2 C, taken October 15, 1929, softening continued to take place throughout the lower portion of the left lung, where several cavities seems to be in process of forming. In December patient began to have chills and increased symptoms of prostration: drenching sweats; appetite and digestion poor; increase in temperature, and the cavities in the lung were more definite, as shown in film Fig. 2 D, taken December 2, 1929. Whether this will continue and cause the death of the patient, or whether after excavating the lower lobe she will improve, remains to be determined.*

I should like to call attention to the disparity between pulse and temperature throughout the course of the disease. A relative bradycardia is present, indicating a preponderant action of the vagus in spite of the severe stimulation of the sympathetics caused by the toxemia.

In comparing the temperature curve, the symptoms as here recited, and the exent and severity of the lesion, as indicated by the plates, it will be seen that the patient had fewer symptoms, and lower temperature, with a severe and more widespread lesion than she had originally, with a more limited lesion. In explanation of this, we must assume that it was due to the establishment of a strong immunity to both tuberculoprotein and to whatever protein was derived from the destroyed lung tissue; otherwise, there is no explanation of her ability to

*Patient has continued to run the same temperature of 100-101° and maintains same general condition. Aug. 10, 1930.

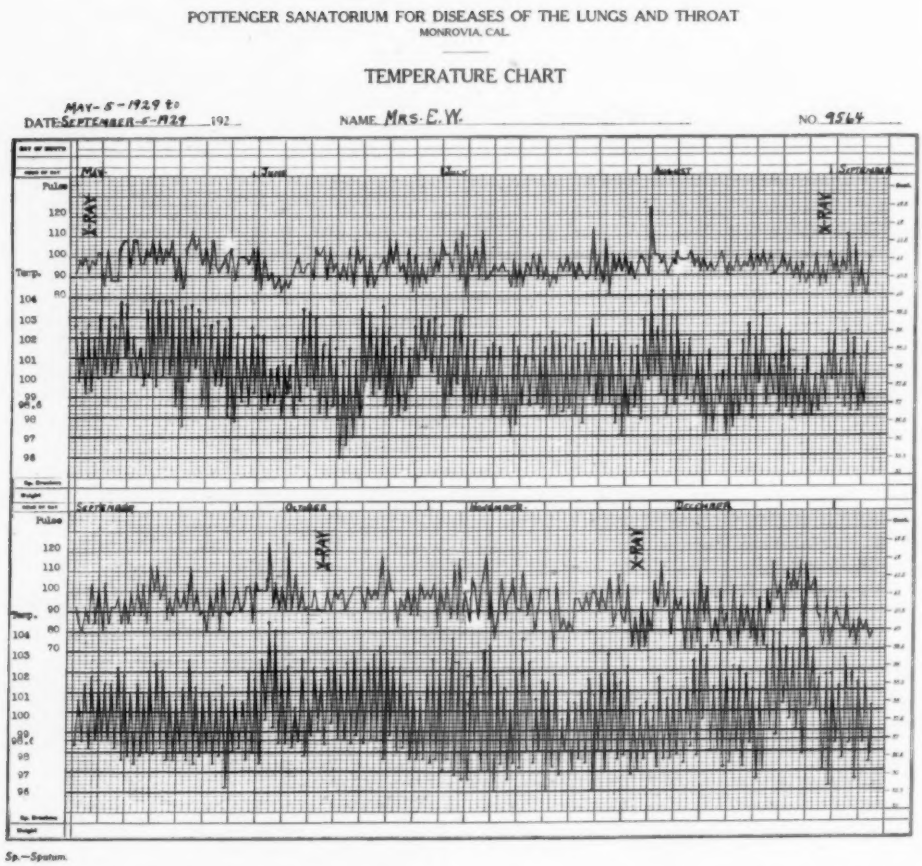
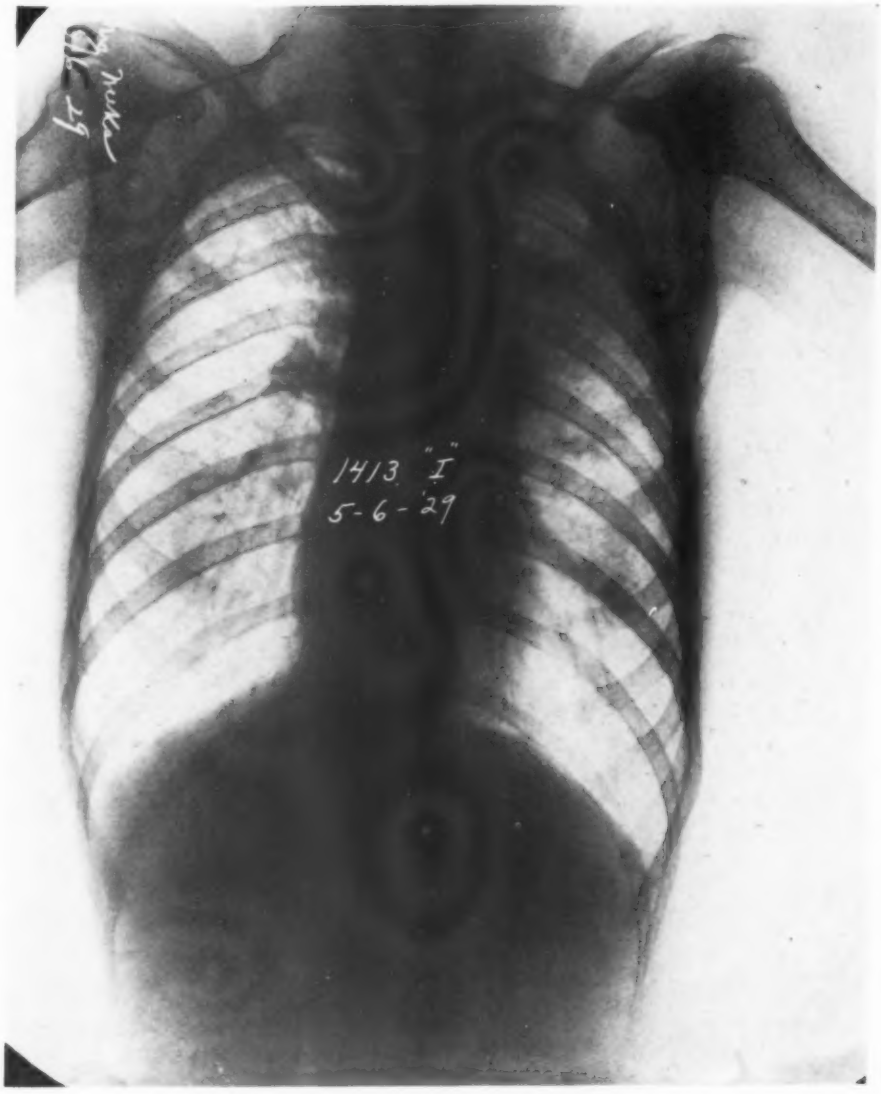



FIG. 1. Temperature and pulse curve of patient suffering from chronic exudative tuberculosis, involving at first the upper two-thirds of left lung, most extensive above the third rib, with cavity in first interspace. Slight involvement in right lung. Patient profoundly toxic. Disease extended and cavitation increased, as will be seen in Fig. 2 A, B, C, and D. The temperature, however, lowered somewhat (fig. 1) as did all symptoms of toxemia; appetite improved, patient was less nervous and sweats disappeared. This condition continued until December 1929, in spite of the extensive disease, as shown in Fig. 2 B, C, and D. Then resistance began to lower, the disease spread, and symptoms of toxemia again increased. The lessening of symptoms, regardless of an extending and destructive process, as indicated by Figs. 1 and 2, suggest that desensitization to both tuberculotoxins and the toxins from the patient's own broken-down tissue must take place.

Note the vagus effect on the pulse. The pulse is relatively slow for the amount of toxemia present.




FIGS. 2 A, B, C, and D illustrate an extensive exudative lesion with cavity, followed by extension and increased cavitation. The toxic symptoms, however, were much greater at first, with the limited amount of disease shown in Fig. 2 A, than they were later, as shown in Fig. 2 A, B, C, and D, although the disease has extended and cavitation had decreased. The temperature curve is shown by chart, Fig. 1.

FIG. 2 A, May 6, 1929, shows a moderate infiltration in the upper half of left lung, with cavity near apex; slight lesion in upper right.

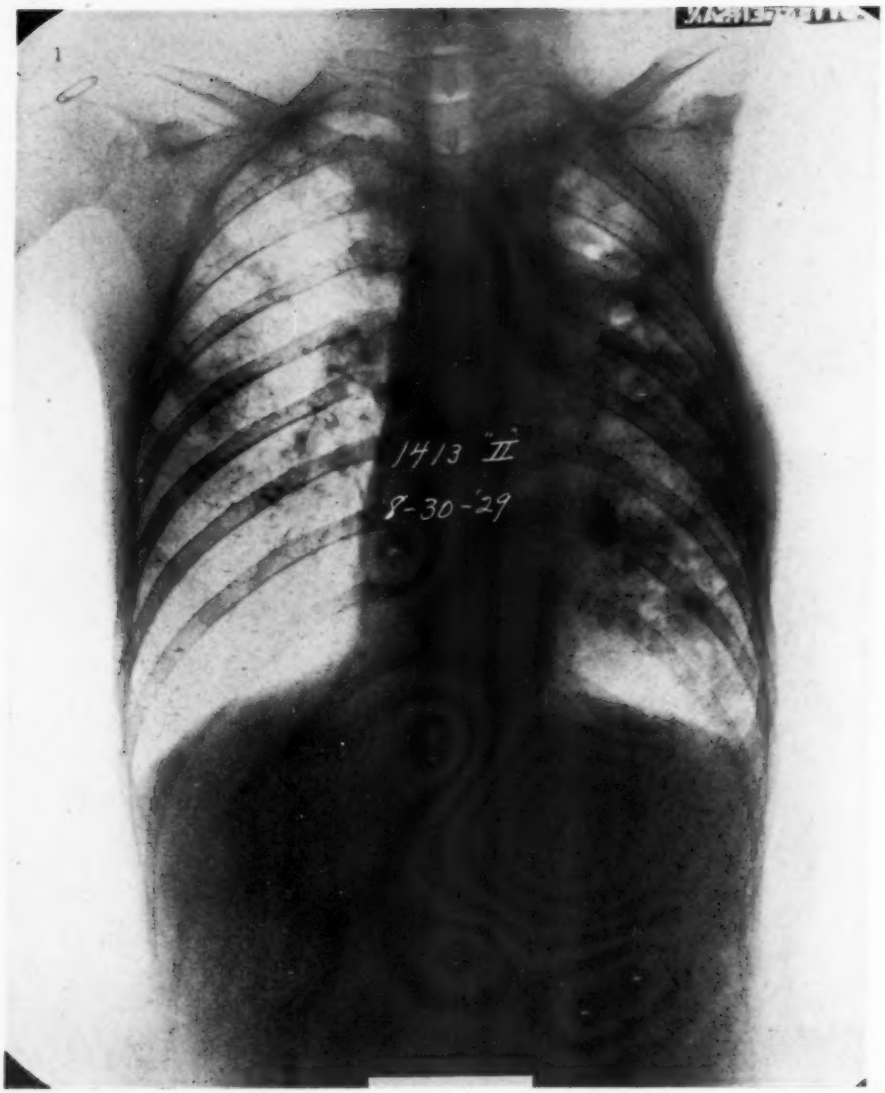



FIG. 2 B, August 30, 1929, shows entire left lung involved with increased softening.

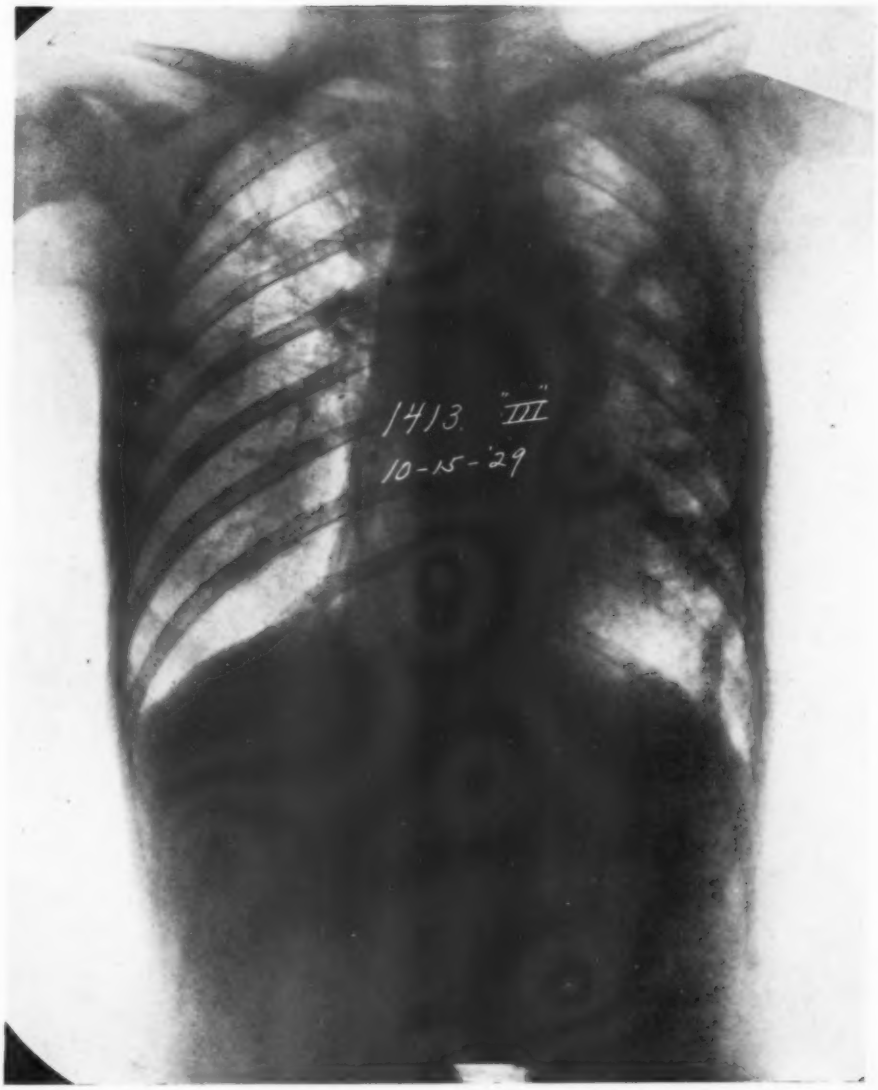



FIG. 3 C, October 15, 1929, shows softening continued to take place throughout the left lung, where several cavities are in the process of forming.

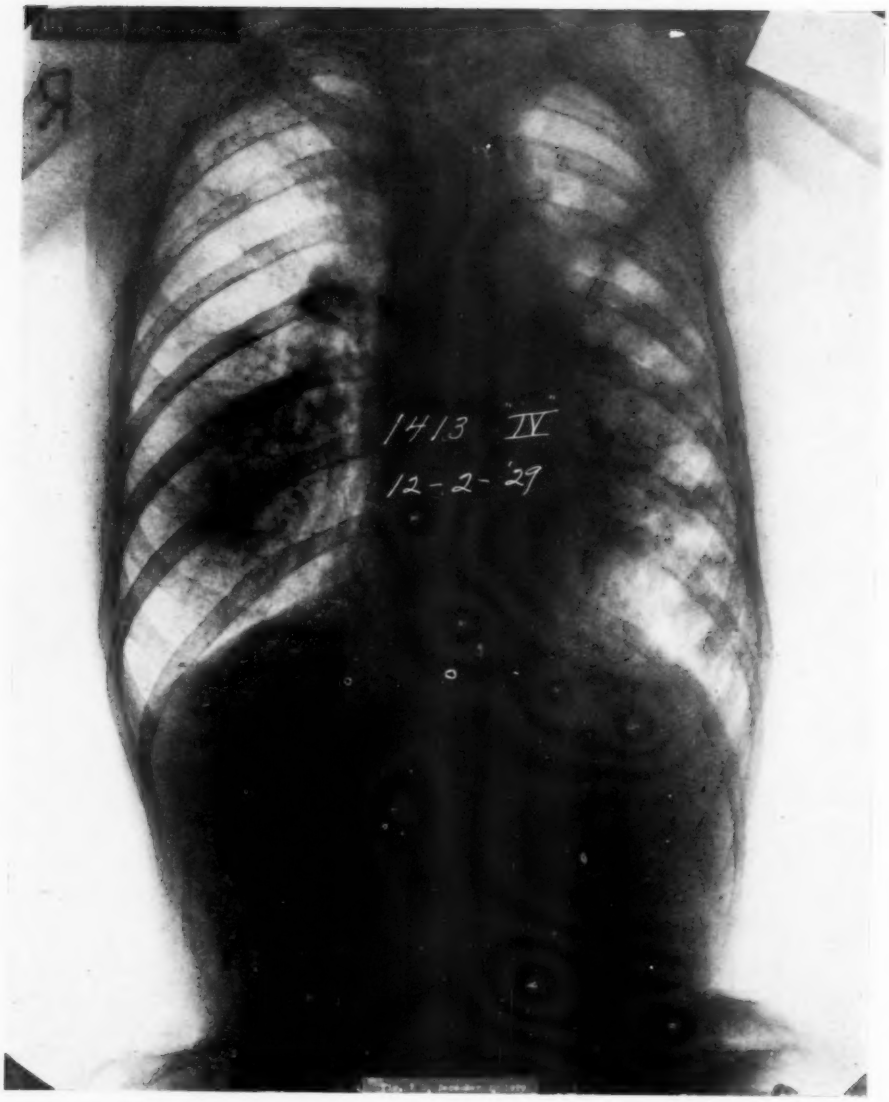



FIG. 2 D, December 2, 1929, shows extensive cavitation throughout left lung.

improve her general physiologic activity while the disease was spreading and showing increased activity pathologically. Desensitization to the patient's own tuberculoprotein, and to whatever other protein was thrown into the system from the broken down lung tissue, is a condition necessary to the understanding of the apparently paradoxical relation between the advancing disease and the lessening of symptoms. Another very interesting thing which suggests the existence of a high degree of specific protection (immunity) is the failure of the disease in the right lung to extend, and a failure of the large quantities of tuberculoprotein which must have been thrown into the blood stream during this time, to cause sufficient reaction to produce marked exudation and caseation in the upper right lung.

*Encapsulation and Rendering Inactive Viable Bacilli.* Encapsulation is one method by which the host renders bacilli harmless though remaining within the body. The condition precedent to such a favorable procedure is that the numbers of bacilli be few; so few that they fail to produce sufficient reaction to cause more than a temporary exudation or more than a very slight necrosis. When extensive necrosis, with loss of much tissue, has once taken place then a replacement must be brought about, and this must be preceded by the elimination of most of the bacilli from the caseous focus and the regeneration of the destroyed tissues. So healing under these circumstances is more complicated.

Attention must also be called to the fact which has been pointed out by Bartel,[19] Opie,[20] and others, that bacilli may remain in the tissues, maintained in a viable though inactive state, for long periods of time. This must be due to another phase of specific defense though as yet there seems no adequate explanation for it.

*The Elimination of Products of Inflammation.* Exudation of some degree is the part of every active tuberculous process. Healing can not be said to have taken place until all exudative phenomena have disappeared. According to the severity of the lesion, exudation may mean only a slight hyperemia, or it may mean the pouring out of serum, cells and fibrin in the tissue. In clearing the field for healing it is necessary to have all such products rendered absorbable or in a condition to be dealt with by the phagocytes. Purely exudative phenomena accompanying tuberculosis clear away by resolution, the same as occurs in acute pneumonia, except a much longer time is required. Should irritation reach a certain degree, however, when resolution has been completed, changes of a proliferative type will be necessary to complete the healing process.

*The Repair of Injury Done.* If the lesion is caused by only a few bacilli, the destruction of tissue is negligible and healing is a comparatively simple process. If the lesion is a slowly advancing one, and caused by the repetition of many small inoculations, the necessary amount of injury may be brought about to disturb the patient's physiologic activity before sufficient specific resistance has been engendered to overcome the infection, and still there be a minimum of tissue loss.

Lesions produced by many bacilli, or bacilli of high virulence, in patients with highly sensitized cells, on the other hand, create conditions which

are markedly inflammatory and often destructive in character from the very beginning; and require a complicated program of resolution and tissue regeneration to repair the damage which has been done. Bacilli and the various inflammatory elements are subjected to enzyme action, and phagocytosis until the field is relieved of all abnormal debris; and then if destruction has taken place, repair follows the usual pathological course of regeneration, being modified of course by the fact that healing must often be accomplished while viable bacilli remain embedded in the tissues. Even cavities of considerable size may be healed at times with a regeneration of tissue.

*How Therapeutic Measures Aid the Process of Healing.*

Healing depends on the power of the patient to meet successfully the various requirements of his own particular infection, no matter what they may be. Therefore, measures of therapy have been devised which have for their purpose the creating of the best possible physiologic balance on the part of each individual patient, and the keeping of his infection quantitatively and qualitatively as mild as possible.

The hygienic life which is pursued by the tuberculous patient has for its purpose the making of the physical and psychical machines to function as perfectly as possible. The most perfect metabolism consistent with the disease is thus brought about and, if maintained for a long period of time, guarantees the maximum protective response on the part of the patient.

Rest is not the ideal status of any individual for a prolonged period of time, but in tuberculosis it is a matter of necessity. [21] The eight or nine hours of daily rest which is capable of maintaining the physiologic balance of the body cells in states of health is wholly inadequate in tuberculosis. In the treatment of tuberculosis we often find it necessary to maintain rest for the entire twenty-four hours for long periods of time—sometimes for many months—because we have a departure from the normal status of such a nature that exercise during the stage of active disease favors extension of infection, increase of toxemia, and lowers resistance, causing the patient's body functions to be carried on at a low standard of efficiency. These factors interfere with healing.

This is where rest to the lung, such as comes from body rest, and such local measures as compression by weights such as shot bags, strapping, operations on the phrenic nerve, pulmonary compression, whether by pneumothorax, or thoracoplasty, are of value. They all serve the purpose of giving the lung more rest, of causing less blood to pass through the diseased areas, and of limiting the motion of the lung to the lowest body demands. The simpler of these measures prove to be satisfactory in a very large percentage of limited lesions and the more elaborate ones are successful in many of the serious ones.

While we are not able to say that scientific knowledge has advanced to the place where we can claim the attainment of a specific diet, we have learned that a well balanced diet containing not only adequate calories but

also vitamins and salts in ample amounts is necessary to the best progress against tuberculosis. The Sauerbruch[22 23 24] diet has seemed to be of decided advantage in tuberculosis of the skin; but, so far, not much has been claimed for it in diseases of the pulmonary form. But it has long been recognized that the patient who is a poor eater and unable to take a well balanced diet rarely makes a satisfactory progress in the healing of tuberculosis.

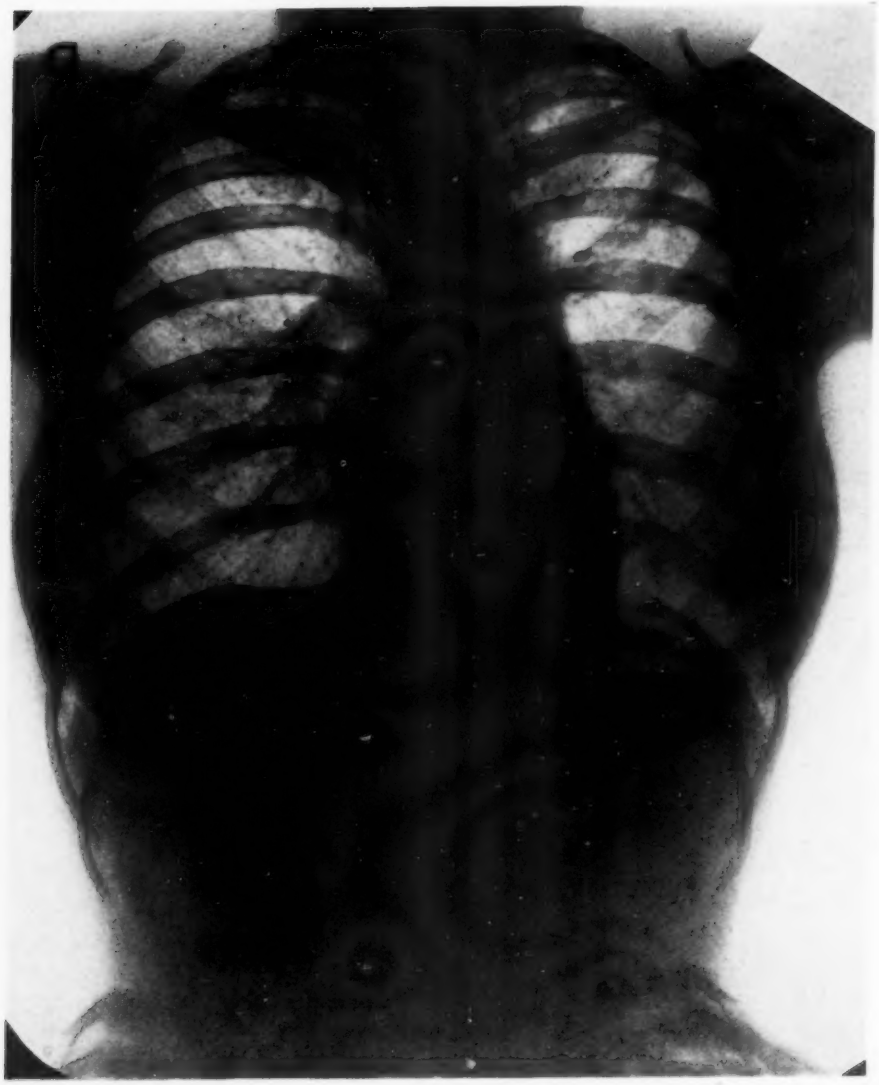
From the discussion above it is clear that it is the mild infections which disturb the patient least and are easiest to overcome, and that it is the severe ones which are dangerous. Larger infections are more dangerous to the patient because they cause more acute inflammatory and destructive reactions, multiply the foci from which extensions may take place, and increase the toxemia which the patient is obliged to combat.

Anything that will increase the likelihood of the disease extending or of carrying the tissue reaction beyond the limits of safety are prejudicial to recovery. On the other hand, anything that will decrease the number of extensions, tend to hold their severity to a low limit, and make the patient more tolerant of toxins and stimulate perifocal fibrosis, will aid recovery.

In the final analysis the patient, if healed at all, is healed by his immunity mechanism. The effect of the patient's own reinoculations of bacilli or bacillary protein are helpful in promoting healing unless they are too severe; but if very severe, they may be harmful; but that he could not attain the necessary immunity to heal without them must be evident to all careful students of the immunological reactions in tuberculosis. It is his reinoculations that, acting on his sensitized cells, cause the allergic inflammatory reactions which result in restraining the passage of bacilli through his tissues, in stimulating the bactericidal properties of the tissues, in desensitizing the patient to the poisonous proteins, and in stimulating the perifocal cells to the formation of fibrous tissue. Whether the patient wills it or not, he is treated and aided in cure by his own tuberculin, as has been stated by Long,[25] and retarded in healing only if the dosage be exceeding large. Therefore, the necessity of tuberculoprotein reinoculations is obvious, but the necessity of keeping them within bounds is equally obvious.

The following cases, whose clinical progress may be judged from the plates and the appended charts, illustrate the principles discussed in the preceding pages.

The plates shown in Figs. 3 and 4 both represent limited apical lesions, one of which healed promptly under the usual sanatorium regime, the other only after compression therapy had been employed. The difference in time of healing in these two patients was probably due to differences in their respective resistance, which probably means differences in the physiochemical reaction of their body cells. There is no evidence of virulent infection in either case; neither is there evidence of spread, aside from that noted in Fig. 2 C; but there is a great difference in the time of healing; the case represented by Fig. 3 requiring a year, and that represented by Fig. 4



FIGS. 3 A and B illustrate healing of early infiltration with almost complete resolution.

FIG. 3 A, June 26, 1928, shows moderate infiltration of the upper half of left lung and apex of right lung.

FIG. 3 B, January 10, 1930, eighteen months later, shows almost complete disappearance of lesion.

requiring three and one-half years to complete the healing.

*Case* No. 9026. Miss A. C. Fig. 3 A and B, are films of a patient with an early tuberculosis involvement of both apices. She came under my care June 26, 1928. Film A shows the involvement at the beginning of treatment. Film B, taken January 10, 1930, shows how completely the lung had cleared. This patient was under treatment from June 26, 1928 until August 23, 1929. She had been away from the sanatorium four and one-half months, when film B was taken.

*Case* No. 9481. Mr. E. P. Fig. 4 A, B, C, and D, are films of a patient with slight involvement of the left apex, who came under my observation May 17, 1926. Film A shows involvement at beginning of treatment. He had not been able to clear the lung in fourteen months' time, as will be shown in film B, taken July 13, 1927. Two months later, as will be seen in film C, the disease had extended very markedly. An exudative lesion is seen through the upper half of the left lung. On account of the apparent lack of resistance on the part of the patient, we considered it necessary to institute artificial pneumothorax, which resulted in a healing, as shown in film D, taken November 12, 1929.

Figs. 5 and 6 represent tuberculosis with acute onset in which cavity was formed very shortly after the first symptoms appeared. Cases such as these have been recently described by Redeker. He recommends that they be treated by the immediate institution of pneumothorax, because he believes that otherwise they will usually fail to heal. We have found, on the contrary, that these lesions usually heal satisfactorily by rest and the regular sanatorium regime, provided treatment is started at once. The healing is by resolution and a mild degree of fibrosis, except in case of the cavity which requires the formation of considerable fibrous tissue. The cavity that heals best is the fresh cavity without too much fibrous tissue about it. Immediate treatment is essential to the successful handling of these cases.

*Case* No. 9388. Miss R. M. Fig. 5 A, B, and C, are films of a patient with acute onset in which the process was preponderantly exudative in type, with cavity formation within three weeks after the onset of clinical symptoms. The patient was apparently in perfect health when she was taken ill with influenza on Thanksgiving day, 1928. She was examined by me in less than three weeks following the onset of influenza, and gave the picture as shown in Fig. 3 A, taken December 18, 1928. This process, under rest and other sanatorium measures went on to a satisfactory healing, the progress of which is shown in film B, taken August 8, 1929, and film C, taken January 1930.

*Case* No. 9679. Miss G. M. Fig. 6 A and B, represents a similar acute process. Patient gives history of dieting for overweight until August 7, 1929, when she had two teeth removed and failed to regain her usual health thereafter. In September she noticed a cough with expectoration, and a temperature of 101°, and severe pain over the right lung. On October 13, the film shown in Fig. 4 A was taken, in which there is an extensive right-sided involvement, with definite cavity formation.

Patient was put on rest and given the usual sanatorium treatment. She had a temperature of 101° for about a month, when it subsided, and with its subsidence the cough and sputum disappeared. Film B, taken on January 13, 1930, shows that the cavity has disappeared. This patient is not yet well, but is rapidly recovering.*

We also see the tendency to heal in many cases which are of longer standing, even though temperature has persisted for a considerable time. The determining factor seems to be the way the patient's physiologic balance is re-

*Aug. 10, 1930 cavity healed.

FIGS. 4 A, B, C, and D show an early apical lesion which failed to heal under ordinary hygienic regimen, but, on the contrary, the disease extended and was healed only after pneumothorax was instituted.

FIG. 4 A, taken May 17, 1926, shows limited lesion of both apices, more marked on the left.

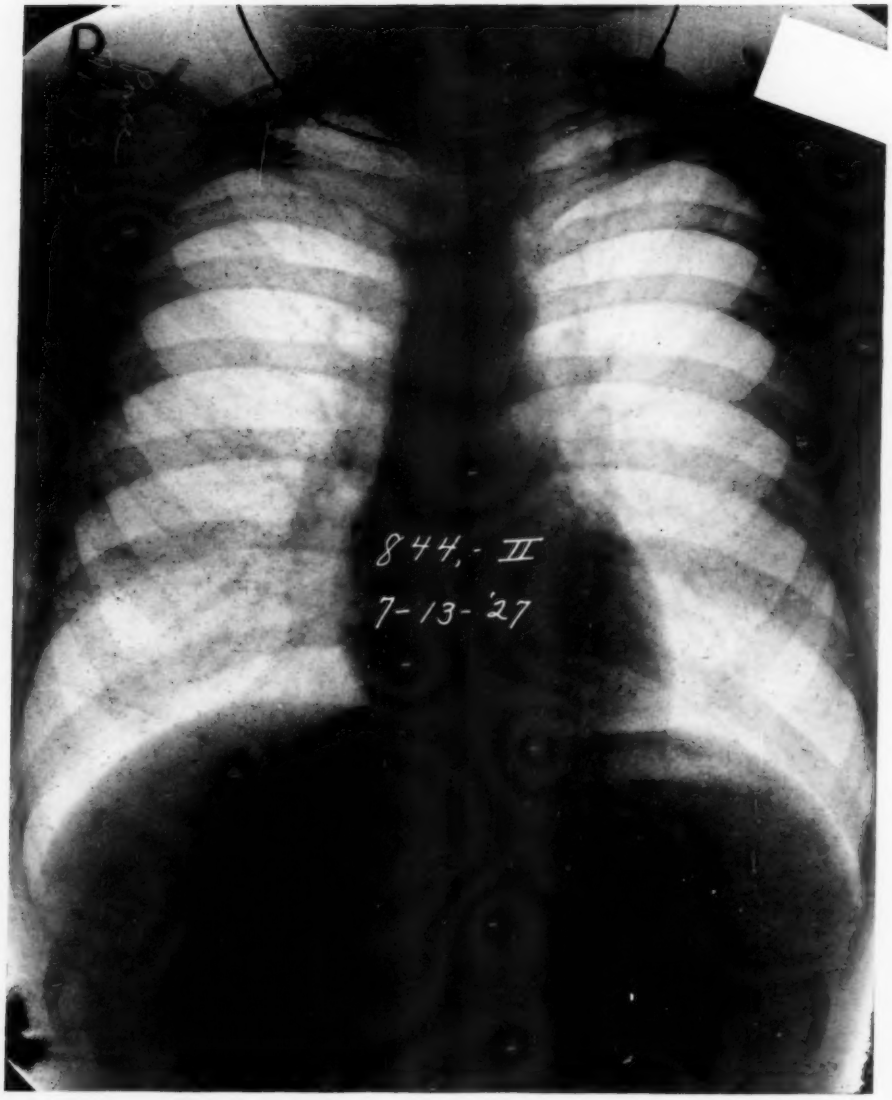
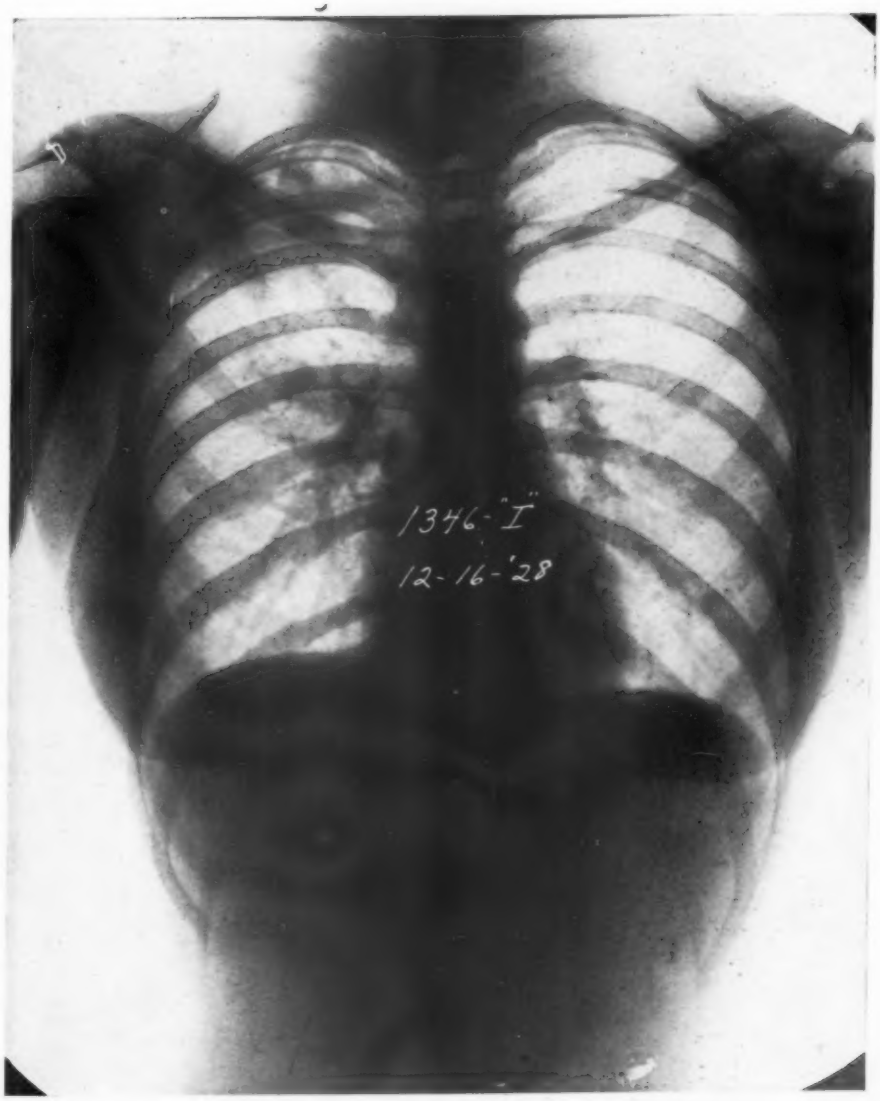



FIG. 4 B, July 13, 1927, twelve months later, shows left apex improved but still unhealed.

FIG. 4 C, September 6, 1927, two months later, shows extension of the disease in left lung. Owing to apparent lack of resistance on part of patient the lung was collapsed.

FIG. 4 D, November 12, 1929, shows apex fairly clear, but lung still unexpanded. Patient symptom free.




FIGS. 5 A, B and C represent an early exudative lesion with rapid cavity formation, which healed under regular sanatorium regime, without mechanical interference. Three weeks before onset of symptoms patient was attending High School. An attack of influenza was accountable for the acute onset of tuberculosis. Sputum became negative.

FIG. 5 A, December 16, 1928, shows acute exudative infiltration in the upper third of right lung, with cavity formation.

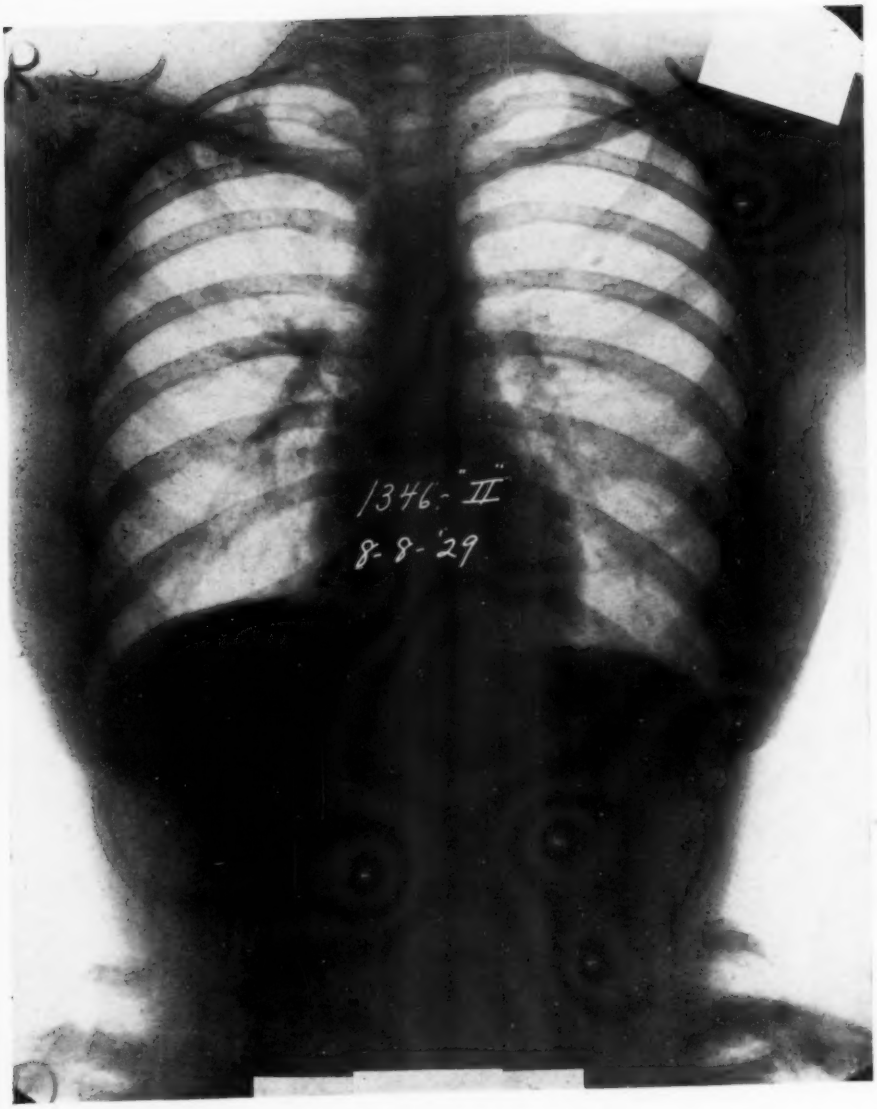



FIG. 5 B, August 8, 1929, shows cavity healing.

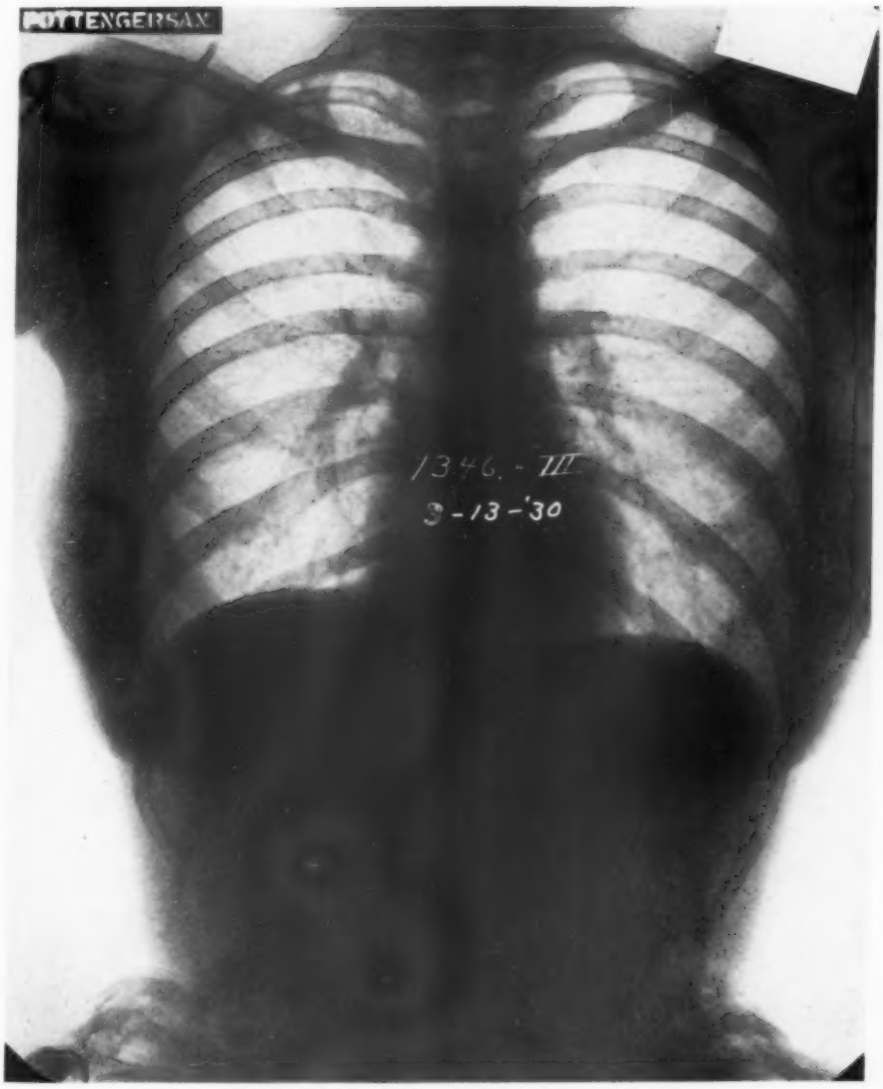



FIG. 5 C, March 13, 19930, shows cavity healed.

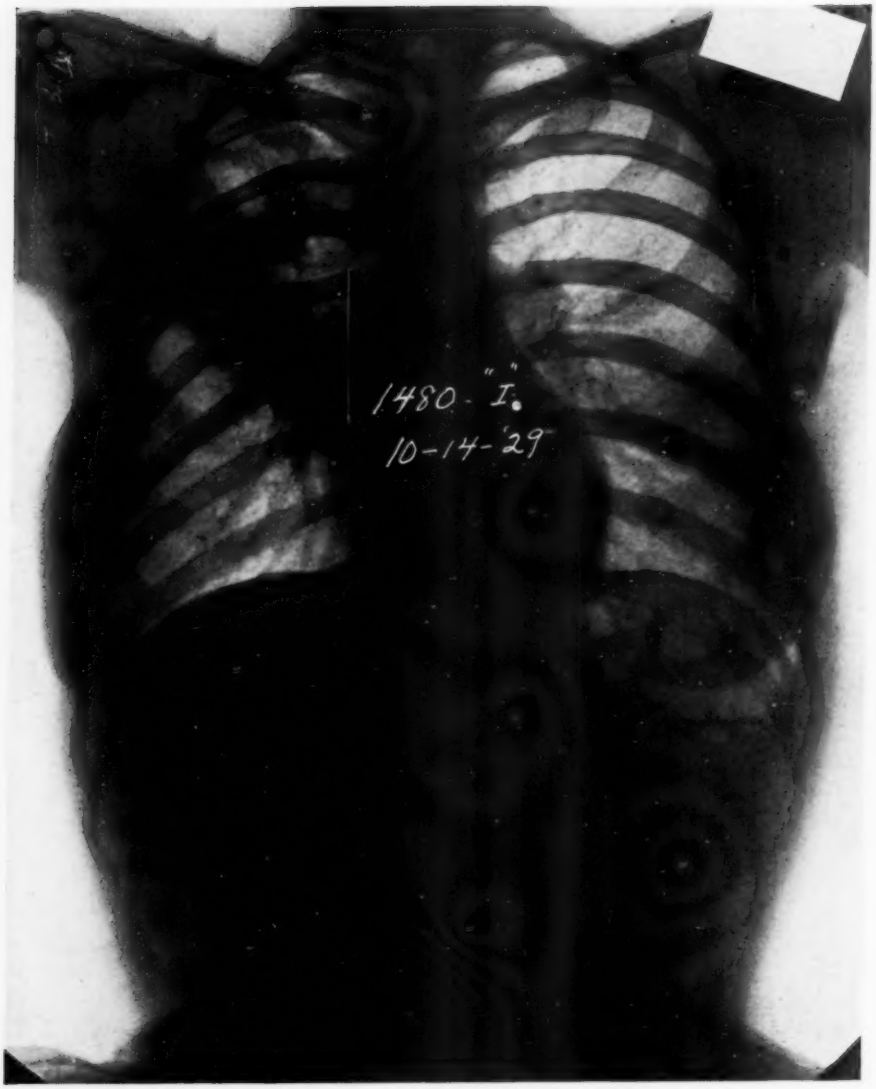



FIG. 6 illustrates the healing of acute exudative tuberculosis with subclavicular cavity, under regular sanatorium regimen, without mechanical interference of any kind. Sputum became negative.

FIG. 6 A, October 14, 1929, shows very extensive infiltration of the upper half of right lung, with cavity.

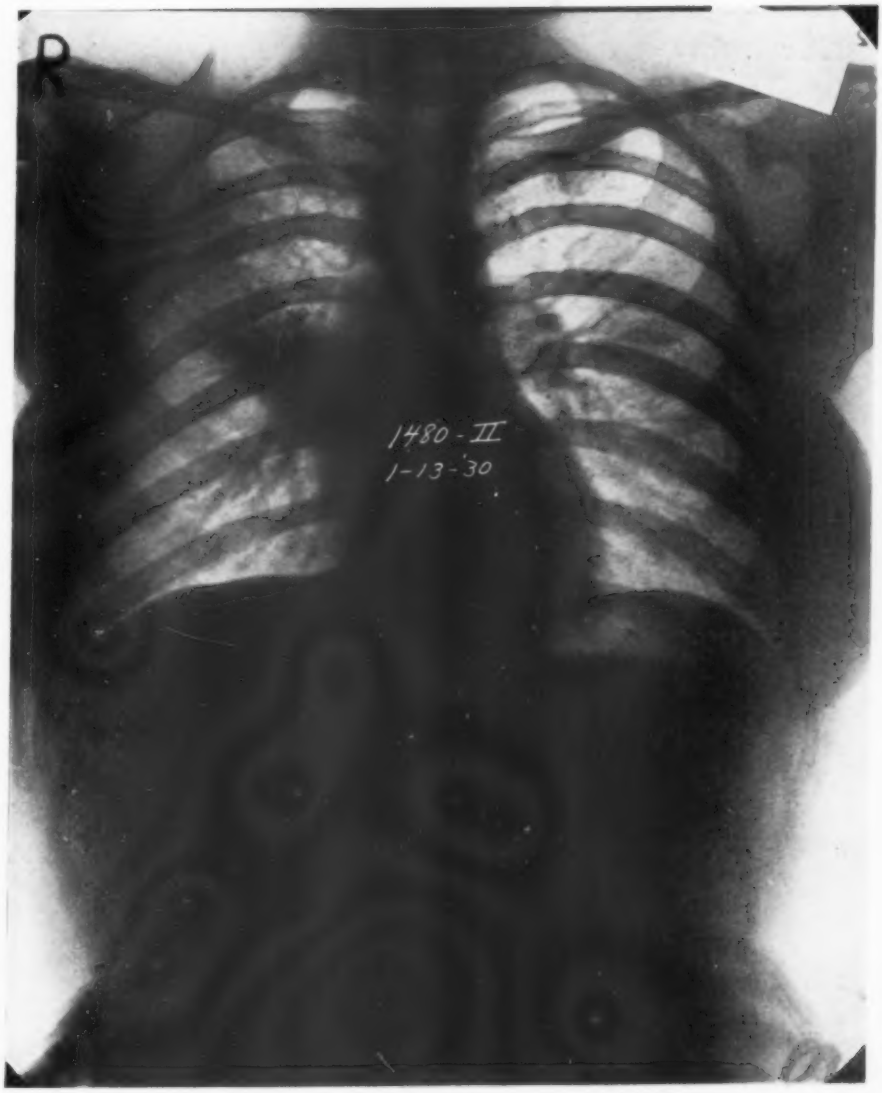



FIG. 6 B, January 13, 1930, shows cavity disappearing and healing progressing satisfactorily.

stored, together with the degree of specific defense that he is able to establish.

*Case* No. 9395. Mr. S. H. Fig. 7 A, B, C, and D, illustrates an advanced combined proliferative and exudative lesion with excavation. The patient entered the sanatorium on December 28, 1928. He had been treated by me for an early tuberculosis occupying the upper portion of the right lung, some six years before, and had made a recovery. In July 1928 he had an acute respiratory infection, accompanied by high temperature, which was diagnosed as influenza. Recovery was slow. After recovery from the influenza he again had a rise of temperature accompanied by a persistent cough and expectoration. Failing to make satisfactory improvement he was sent to the sanatorium, with the condition as shown in film A. There are several areas of loss of tissue in the upper half of the right lung. In his temperature chart, shown in Fig. 8, it will be noticed that during the first six months he had considerable elevation of temperature. Film B, taken February 8, 1929, shows a slight increase in the exudative character of the lesion, but no increase in destruction of tissue. Film C, taken May 10, 1919, shows a very marked increase in the exudative type of the lesion, but a general improvement in the areas of involvement in the second and third interspaces. These changes had taken place during a course of continuous temperature, which we assume accompanied repeated reinoculations of bacilli and bacillary protein, as will be seen in Fig. 8. Shortly after this all appreciable reinoculations ceased; the temperature came to normal; the tuberculous inflammation proceeded to heal by resolution and fibrosis. Film D, taken January 22, 1930, shows the extent to which the right lung has cleared to date.

The clinical improvement in this case was exceptionally gratifying. Upon entering the sanatorium his sputum was 160 cc in 24 hours, with 250 tubercle bacilli per microscopic field. At the time film B was taken, it was 150 cc in 24 hours, with 100 tubercle bacilli per microscopic field. When film C was taken it had dropped to 65 cc in 24 hours, with 6 tubercle bacilli per microscopic field. When film D was taken it was 2 cc in 24 hours, with 30 tubercle bacilli per microscopic field. While the lesion is not quite healed, yet it is rapidly approaching that state. This shows that a far advanced destructive lesion can be turned to a favorable ending, provided cooperation can be had for a sufficient length of time.*

Patients who show a preponderantly exudative reaction are usually considered as belonging to a more serious group, but they too will often heal even though the disease is widespread.

*Case* 7670. Mrs. W. J. Fig. 9 A and B, illustrates an extensive fibrocaseous tuberculosis, with marked allergic reaction causing a severe exudative process. The patient had been ill for more than a year; had lost weight to eighty-five pounds, and had had fever for several months. On entering the sanitorium (Fig. 9, film A) she had a temperature of 101°. The sputum shows 30 cc in 24 hours, with 100 tubercle bacilli per microscopic field.

The patient was under the usual sanatorium treatment. On May 9, 1927, eighteen months later, the lung fields had practically cleared, as shown in film B. At that time she was free from cough, expectoration and tubercle bacilli, and weighed 105 pounds. The case illustrates the natural healing of an extensive lesion largely by resolution.

In cases where a satisfactory physiologic balance can not be restored and immunity can not be built up, the disease will spread in spite of all that can be done. Such patients suffer severe

*Aug. 10, 1930. Now healed and bacillus free.

FIGS. 7 A, B, C, and D illustrate healing of extensive combined proliferative and exudative tuberculosis, with cavity formation, under regular sanatorium regimen, without mechanical interference. The temperature, pulse and weight of this patient are shown in Fig. 8.

FIG. 7 A, December 28, 1928, shows marked involvement of upper two-thirds of right lung; slight involvement in left; multiple cavitation in right.

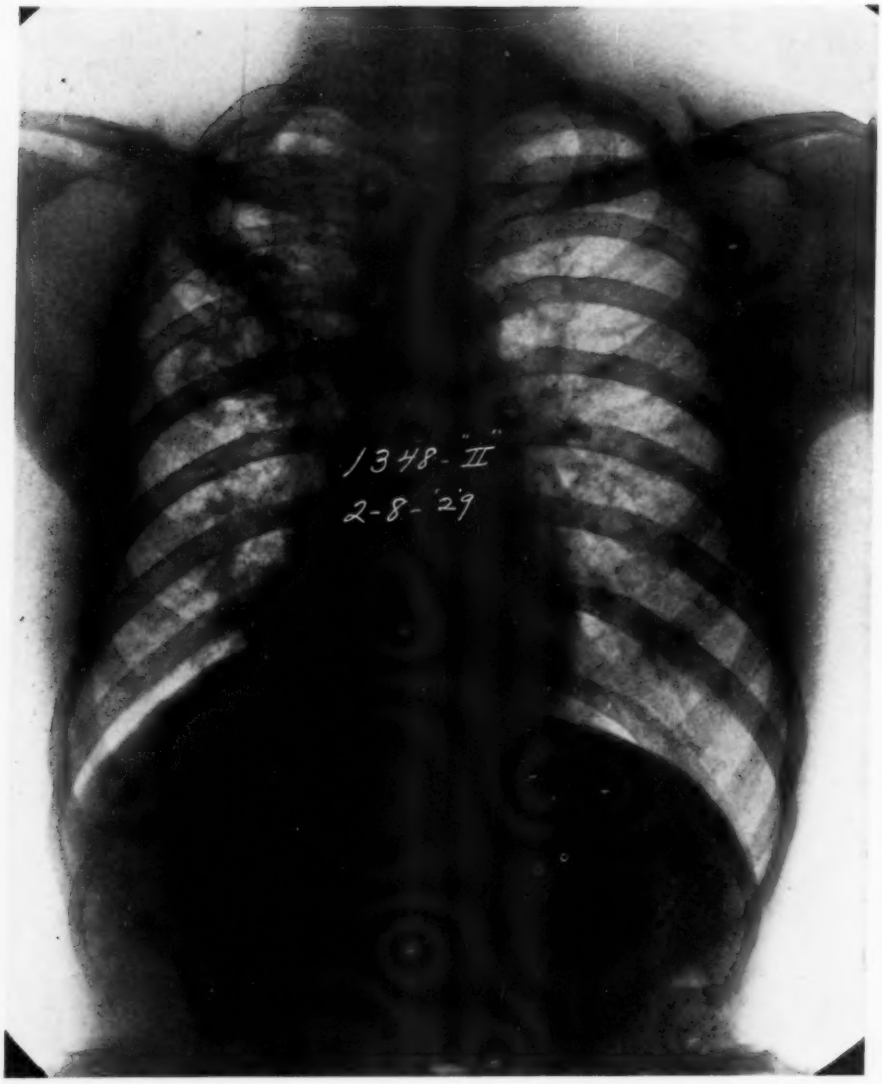



FIG. 7 B, February 8, 1929, shows extension of the disease in lower right lung and also in central portion of left lung. At this time an unsuccessful attempt was made to collapse lung.

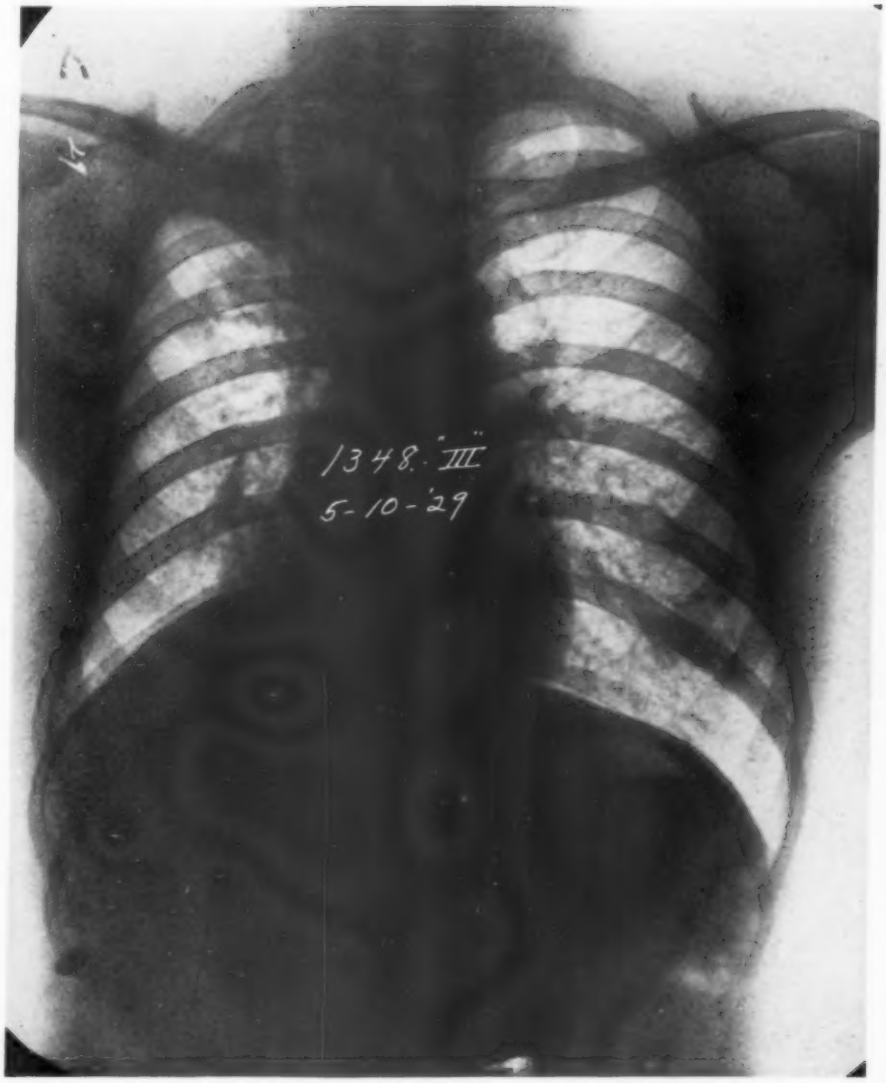



FIG. 7 C, May 10, 1929, shows the beginning of resolution in the middle portion of right lung; pleurisy over the apex.

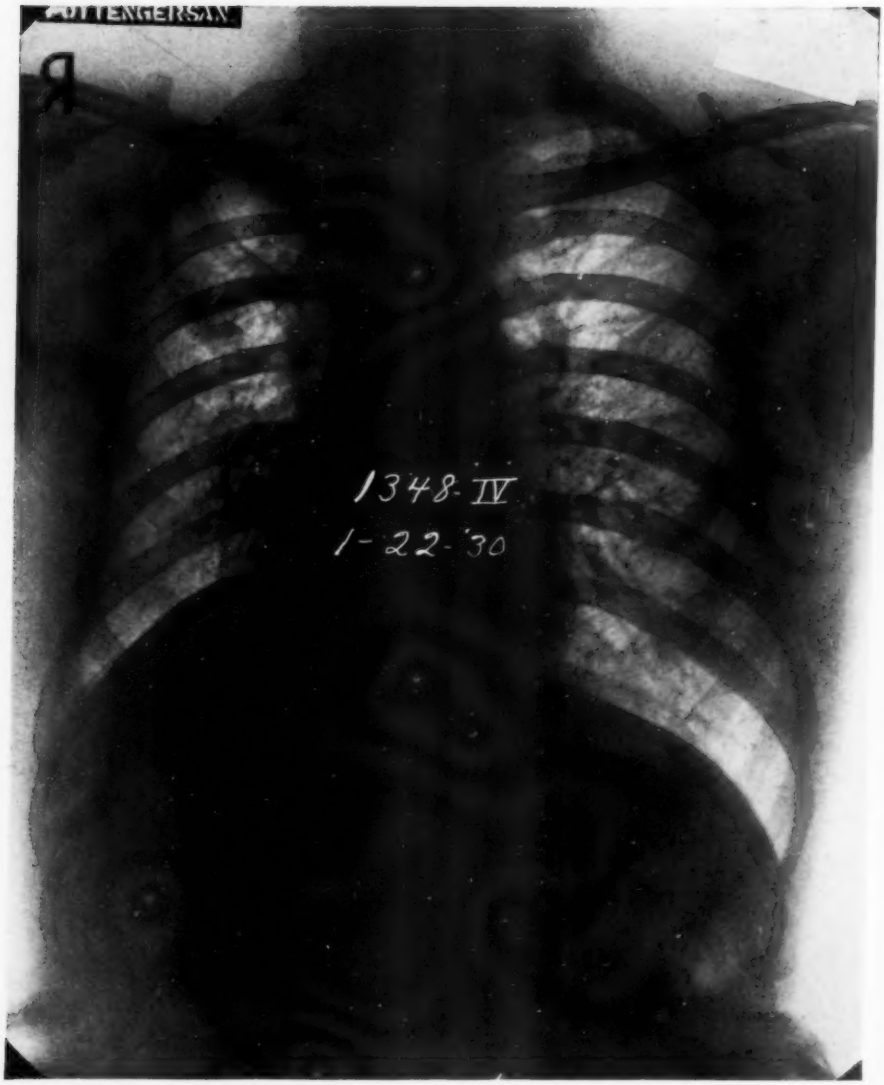
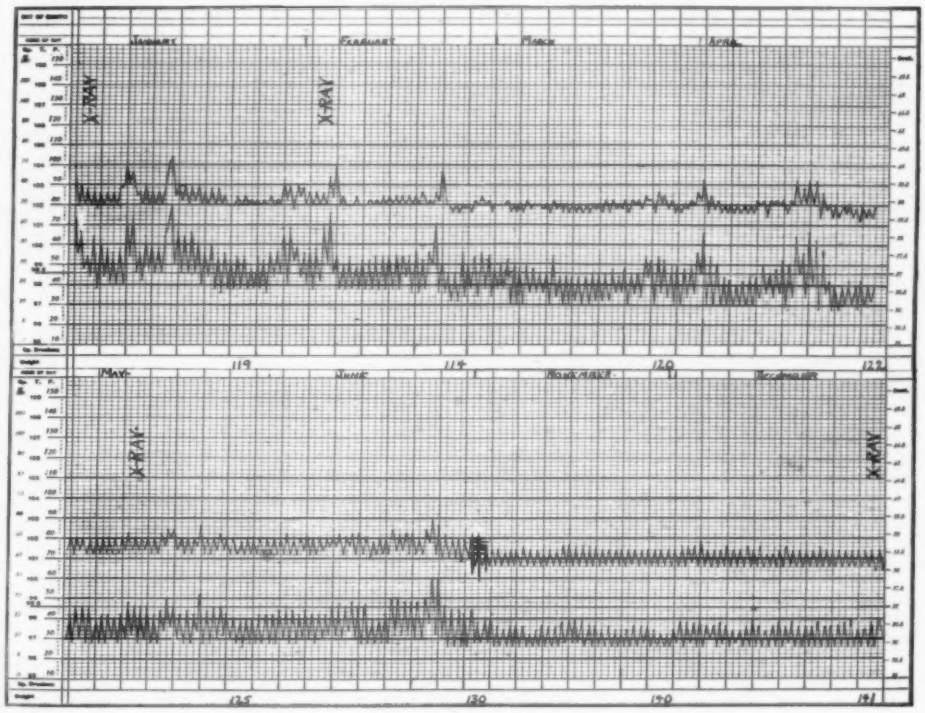



FIG. 7 D, January 22, 1930, shows almost complete absorption of exudate through right lung.

POTTENGER SANATORIUM FOR DISEASES OF THE LUNGS AND THROAT
MONROVIA, CAL.

TEMPERATURE CHART

DECEMBER-27-1928 to
DATE-APRIL-29-1929- 192_ NAME Mr. S.H. NO. 9395



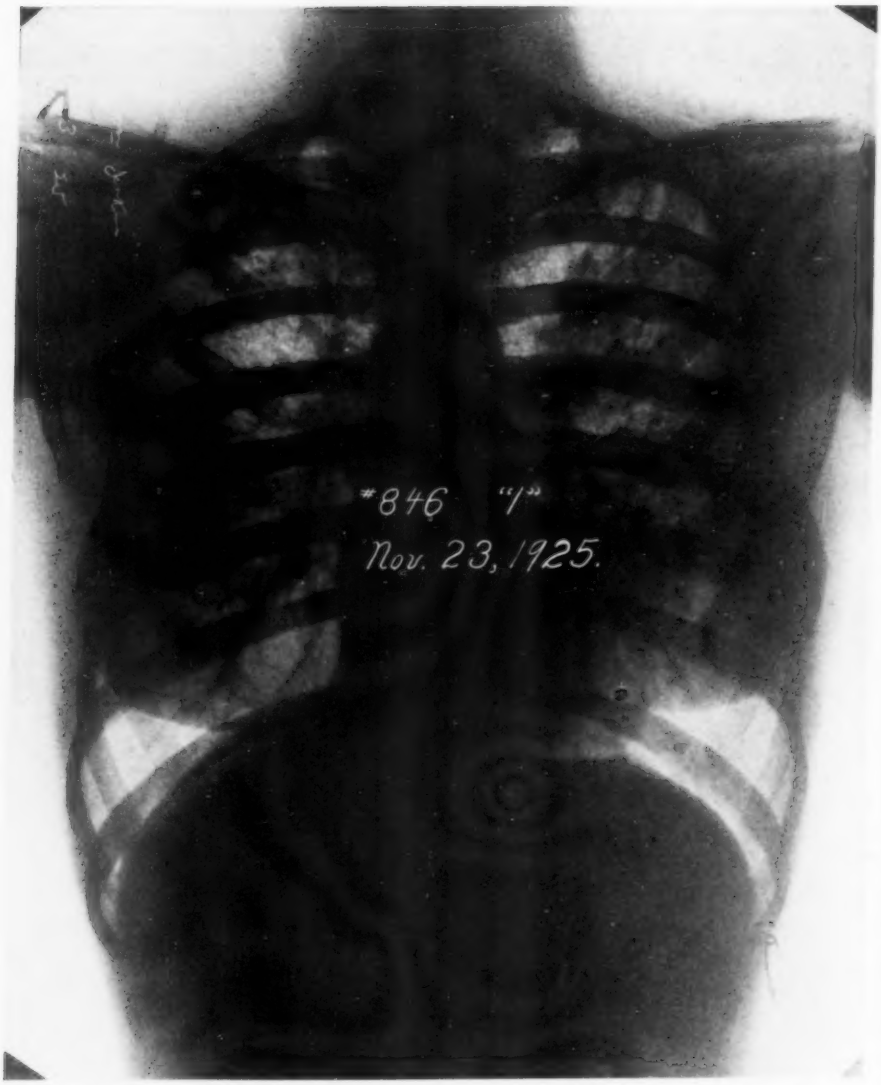

Sp.—Sputum.

Fig. 8 illustrates the temperature and pulse of the patient whose films are shown in Fig. 7 A, B, C and D. Patient had constant temperature during first two months, followed by remission during the third month ;and again followed by two periods of prolonged temperature in the latter half of the third and fourth months.

Temperature then dropped, remaining below normal for the most of the time except during early May and the latter part of June. Temperature again dropped to below normal, where it remained, as is shown in the latter portion of the chart.

Patient's weight decreased from 119 to 114 during the first two months. After that patient made steady gain in weight until 141 lbs. was reached, January 1920.

Sputum, December 1928, 160 cc in 24 hours, with 250 tubercle bacilli per microscopic field; December 1929, 2 cc in 24 hours, with 30 tubercle bacilli per microscopic field.




FIGS. 9 A and B illustrate an extensive fibrocaseous tuberculosis with marked allergic exudative inflammation, which healed under regular sanatorium regimen, without mechanical interference. Sputum became negative.

FIG. 9 A, November 23, 1925, shows extensive exudative process in both lungs.

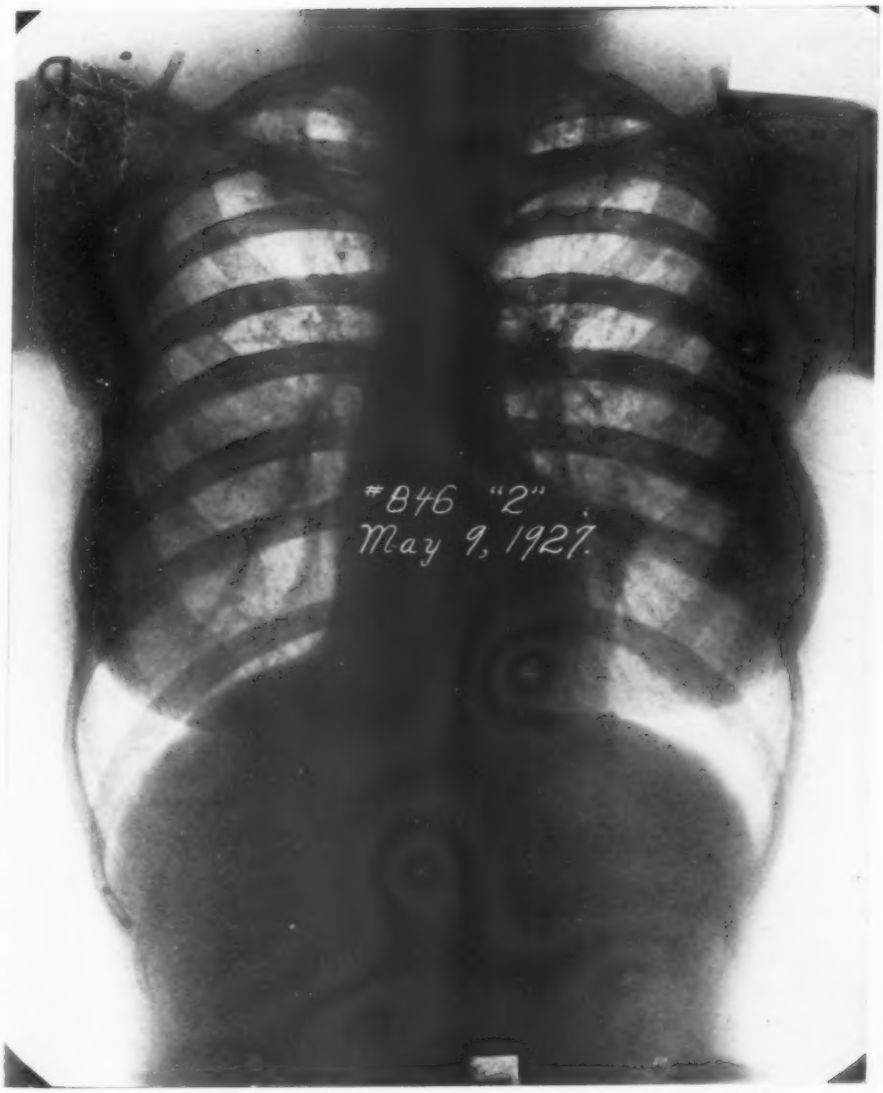



FIG. 9 B. May 9, 1927, shows a very marked clearing, although marked shadow due to proliferative process and also deposits of calcium, remain in the upper portion of both lungs. Marked pleuro-pericardial adhesions on left side will also be noted.

reinoculations accompanied by marked allergic response. Toxicity is marked, and even with moderately low temperature, they continue to show toxic symptoms. Healing under these circumstances usually fails. We must either assume that the lesion is caused by bacilli of unusual virulence, or that the numbers of bacilli in the reinoculations are extremely large, or that the resistance on the part of the individual is very low; or it may be that all of these conditions are present. The case which follows illustrates this type.

*Case* No. 9443. Miss M. W. Fig. 10, A, B, C, and D, illustrates an acute onset with an exudative lesion in the upper portion of the right lung, which went on to cavitation and death of the patient in spite of treatment. This patient had been working up until two weeks before she entered the sanatorium. Film A was taken February 17, 1929, when patient was having considerable temperature. This went on to cavity formation, regardless of treatment, as shown in film B, taken May 20, 1929. Film C, taken August 27, 1929, shows an increase in the exudative reaction in the upper portion of the right lung, and film D, taken October 7, 1929, shows a very extensive excavation of the right apex. It will be noted, however, that in spite of the severity of the disease there was very little extension of infection in the left lung. Not until film D was taken was any particular extension shown, and this was taken only about three weeks before death, following a general breaking down of the patient's resistance.

Preponderantly fibroid lesions are usually spoken of as being the most favorable type. This is probably due to the fact that they exist for a long period of time and are of a milder degree. The difficulty with a preponderantly fibroid type, however, is that the patient is apt to delay treatment until he is seriously handicapped by extensive fibrosis, general emphysema, pleural adhesions, and until the disease is beginning to take upon itself more active and destructive aspects, all of which produce permanent and serious effects. The patient can live comfortably with this form of the disease for a long time, but from the standpoint of healing, it has been my experience that it is not so favorable, or at least not more favorable than the more acute types, because the latter will heal and leave a much freer lung field than the preponderantly fibroid type.

*Case* No. 9438. Mr. A. R. Fig. 11 A, B, and C, represents an extensive lesion preponderantly proliferative in character. This patient had been working continuously, free from symptoms of any character, until a hoarseness was noted, which interfered with his work as a salesman. On consulting a throat specialist, an ulceration was found in the larynx, which involved the cords and arytenoids, and on examination of the chest revealed an extensive lung involvement. The extent of this is shown in Fig. 11, film A, taken February 12, 1929. It will be noticed that there is an exudation of mild degree in numerous areas on this plate, in both lungs, although the process as a whole is preponderantly proliferative. This patient improved satisfactorily under sanitorium regime, as may be inferred from film B, taken August 7, 1929, and film C, taken January 22, 1930.

This case illustrates how the lung fails to clear in a preponderantly proliferative lesion, even though healing has been attained. New tissue has been formed, which replaces the elastic tissue of the normal lung. Although healing is nearly accomplished, as shown in film C, many shadows continue to show. Contrasting this with the preponderantly exudative types Figs. 3, 4 and 9, it will be seen that in

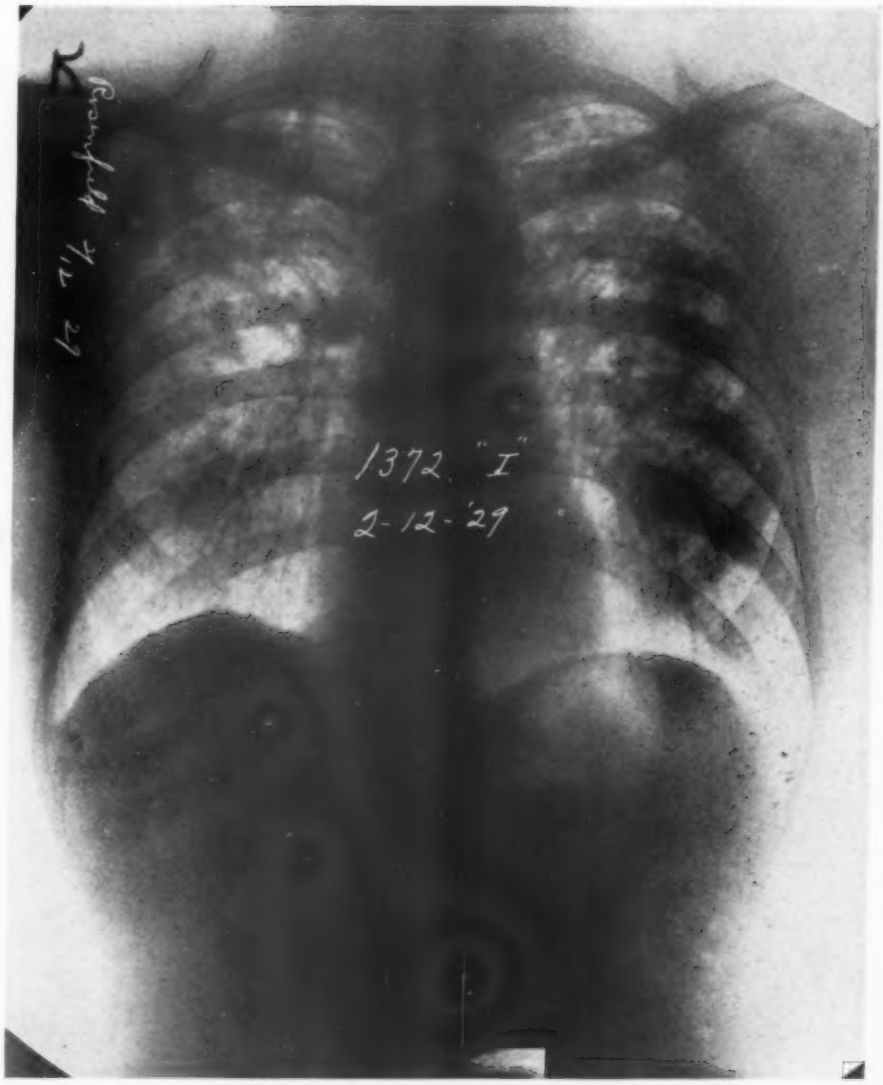
FIGS. 10 A, B, C, and D show an acute exudative lesion involving upper half of right lung and middle portion of left lung, which extended regardless of treatment. Patient died from extension of disease, with meningeal involvement. Patient was not able to muster sufficient resistance to bring the disease to a standstill.

Fig. 10 A, February 17, 1929, shows acute exudative lesion in the upper half of right lung, with cavity formation near apex; a moderate lesion in the middle of left lung. Patient was severely toxic.

FIG. 10 B, May 20, 1929, shows increase in exduation and cavity more definitely formed; lesion in right lung much the same as in Fig. 10 A.

FIG. 10 C, August 27, 1929, shows the lesion still markedly exudative; extension of infiltration in left lung.

FIG. 10 D, October 7, 1929, shows a more definite excavation in upper portion of right lung; some disappearance of the pleural haze; very marked extension in left lung.




FIGS. 11 A, B, and C represent preponderantly proliferative lesion. Regardless of the extent of the lesion, as shown in Fig. 11 A, February 12, 1929, patient did not know he was ill until hoarseness from laryngeal ulceration developed one week previously. Extensive proliferation is shown through the major portion of both lungs, with areas of increased exudation scattered through.

FIG. 11 B, August 7, 1929, shows resolution of a considerable portion of the exudation.

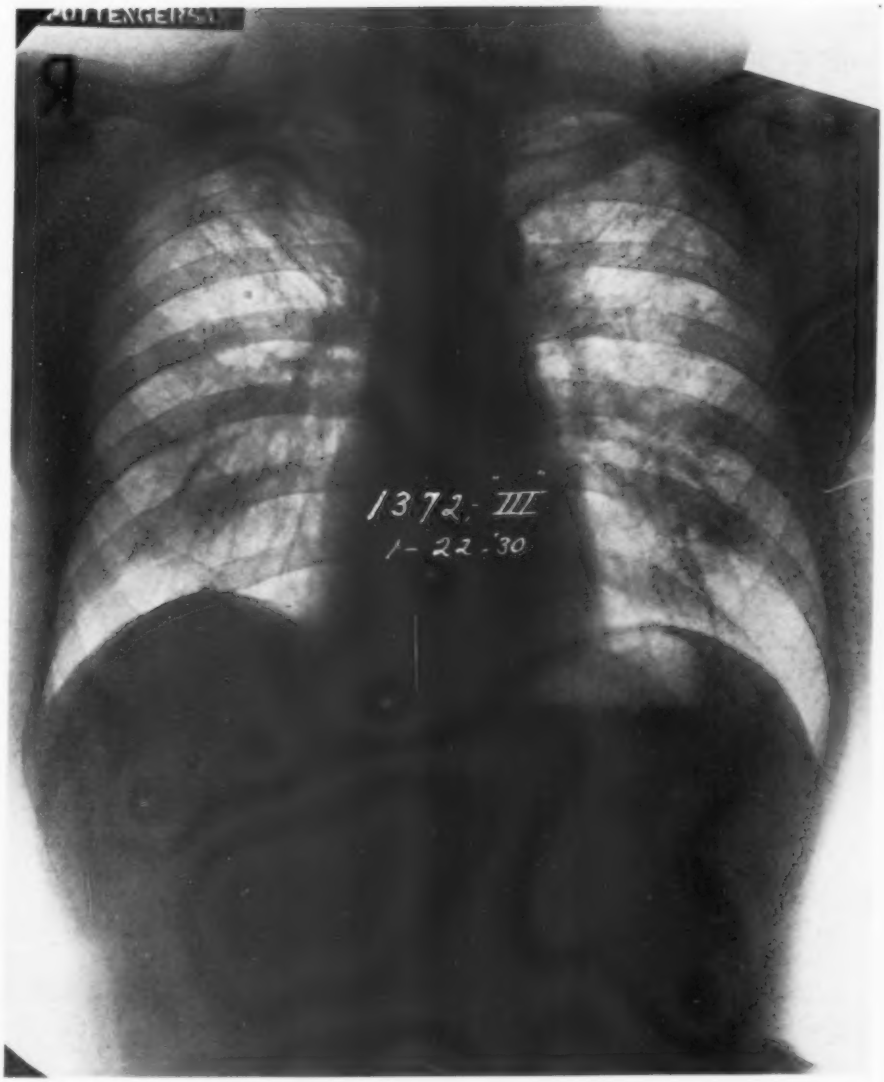



FIG. 11 C, taken January 22, 1930, shows a continued resolution, but the lung fields still show extensive shadows due to the chronic proliferative process. Such lesions leave far more evidence of infection in the lung than do the preponderantly exudative type, which clear largely by resolution.

the latter the lung field clears, leaving very few shadows on the plate.

We are probably justified in assuming that the difference between a preponderantly exudative and a preponderantly proliferative lesion is a difference in the specific defense. In the preponderantly exudative type we have a higher sensitization of cells and a more active allergic reaction. In the preponderantly proliferative type sensitization is much less in evidence and the allergic reaction only takes place to a minimal degree. The difference in the lesions might be due to a difference in the virulence of bacilli, a difference in reaction on the part of the patient, or to the establishment of a more complete immunity, in which sensitization and the allergic inflammatory process take a lesser part. In the preponderantly proliferative group, the toxic symptoms are usually mild, in fact, they are often absent until the disease becomes very extensive; while in the exudative group, the toxic symptoms are marked and come on early.

From these illustrative cases it may readily be seen how tuberculosis tends to heal under favorable conditions; how the patient may become desensitized to his own and to bacillary protein, which enables him to withstand severe disease for long periods of time; and too, how, now and then the disease will spread and cause a severe and fatal illness without calling out an effective specific resistance.

## Summary

1. Tuberculosis heals as a result of the patient's immunity reaction.

2. The efficiency of the immunity reaction is increased by repeated reinoculations.

3. The effects of immunity are shown in the following services rendered to the host:

(a) Destruction of bacilli
(b) Retardation of the passage of bacilli through the tissues
(c) Elimination of bacilli through natural channels by caseation and cavity formation
(d) Development of a state of desensitization to bacillary and non-bacillary toxins.
(e) Encapsulation or rendering inactive viable bacilli which remain in the tissues
(f) Ridding the body of the inflammatory products which accompany the infection
(g) Repair of the injury inflicted upon the body by the disease.

4. Treatment is efficacious to the extent that it is able to limit reinoculations of bacilli and bacillary protein to a minimum and create within the patient a resistance capable of coping with them as they occur.

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# Editorials

## *RECENT STATISTICAL STUDIES OF CANCER PROBLEMS*

Greenwood has reviewed the papers and monographs published within recent years utilizing mainly or wholly a statistical method, which, in his opinion, have advanced our knowledge of some aspect of the problem of malignant disease. As he himself admits the selection of the articles reviewed may be colored by his individual predilection; but it is possible that such a review, however incomplete and even biased, may be interesting and of some service to the general reader. The first topic considered in his review is the alleged increase of cancer. By all lay writers, and a majority of medical writers the recorded increase in the cancer mortality rate has been accepted, if not precisely at its face value, at least as reflecting a substantial change of incidence with time. From this point of view a minority of competent statisticians dissent and endorse the view of King and Newsholme that the recorded increase merely reflects improvement in the certification of causes of death. They argue that the significant increase of cancer mortality is borne by the sites less accessible to examination, and therefore such that diagnosis would become less difficult with the improvement of medical technique and diagnosis. On the other hand, Stevenson has pointed out that neither in English or American experience is it true that the rate of increase in cancer of inaccessible sites has uniformly been greater than that of accessible sites. Schereschewsky and Dublin concluded that when reasonable allowance was made for errors and changes in sex and age constitution of the population a real increase of rate of mortality with time persisted. The balance of opinion inclines towards the conclusion that the rate of mortality from cancer as a whole has really increased. At the same time it is recognized by those who hold that opinion, that in most all countries the recorded changes during the last generation, perhaps, over-state the real change. It is further to be remembered that the increase has affected the older age groups and is coincident with a fall in the mortality rate from all causes together. A larger proportion of persons now live to the "cancer age" who formerly died in earlier life, and the quality of these survivors may be different from that of persons in the decline of life 50 years ago. Greenwood sums up the matter by the statement that it appears that there has been no decrease and probably an increase of the real rate of mortality from cancer, but the records of the

*A Review of Recent Statistical Studies of Cancer Problems. By Major Greenwood (Studies on the Diagnosis and Nature of Cancer. Wm. Wood & Co., 1930, p. 95).

most highly developed systems of vital statistics show that this increase is slowing down. In all countries down to very recent times, the rate of mortality from cancer was returned as being higher among women than men, but this is no longer universally true. There is little doubt that the factor of improved diagnosis, to which the whole increase of cancer mortality has been attributed by some, is partly responsible, since cancers of the breast and uterus which form so important a part of the gross mortality from cancer in women, are relatively easy to diagnose, so that a smaller proportion of missed cases occurred in the past in cancers of females than of males. Modern statistics confirm also the earlier conclusions as to the greater liability of married women to cancers of the uterus than of unmarried. As to the effect of occupation and social status upon cancer mortality, the most recently analyzed figures show a regular increase from the highest to the lower social grading. The class most prosperous shows the lowest cancer mortality. It has further been found that when this social distribution was analyzed as to the different sites of cancer, differentiation proved to be confined to certain sites accounting in all for about half of the total mortality. These sites include the alimentarry tract from mouth to stomach, the skin and the larynx. Sufficient data have not yet been collected to prove the susceptibility or immunity to cancer in different races. This question is still open. A similar uncertainty attends the statistics of cancer mortality as affected by locality. No very definite conclusions have emerged from statistical studies carried out along this line. The same may be said as to the contrasting rates of mortality in villages, streets and houses. The meaning of the apparent bias of the distribution cannot as yet be ascertained. We do not know yet whether certain houses have an apparently undue proportion of deaths from cancer, because there is some peculiarity in the houses themselves, or whether these chanced to be houses occupied by an abnormal proportion of persons living at the cancer age. As to the old idea that a meat diet predisposes to cancer, an enquiry into the cancer mortality among the members of various vegetarian orders showed that cancer undoubtedly occurred in the members of such and that there was no indication that the position of cancer relatively to that of other causes of death was in any way exceptional. This enquiry did not, therefore, confirm the belief that a meat diet predisposes to cancer. Great divergences exist between the rates of mortality from cancer of the female breast and uterus in the three countries, England and Wales, the Netherlands, and Italy. The reason for this divergence has been the object of a prolonged international enquiry carried out under the auspices of the Health Section of the League of Nations by representatives of the three countries. This investigation has thrown much light on related topics but has failed to explain the fundamental differences. Here too, it does not seem that the problem can be solved by means of purely statistical investigation. A good deal of recent

work has been done on the relative frequency of cancer in native races. The general result has been that all forms of malignant disease seen in civilized countries occur in native races, but that the proportional frequencies of different varieties are different. A careful enquiry by Hoffman respecting the incidence of cancer in the American Indian, suggests that the incidence of cancer is low, but fails to establish any definite association between either the consumtption of meat or the prevalence of constipation and the cancer mortalities of different tribes. It is Greenwood's opinion that the data at present available are altogether insufficient to form the basis of any induction. The surgical statistics of cancer have attempted to answer such questions as: What is the average length of life of persons suffering from different forms of malignant disease who are not treated by any method designed to remove the disease? What is the advantage of surgical treatment adopted at different stages of the disease? Comparative advantages of the knife and radiological treatment in different forms and at different stages of cancer? Proportion of cancer cases receiving early treatment, and how may that proportion be increased? From various papers on cancer of the breast and uterus the conclusion may be reached that early radical operation in cancer of the breast means an average prolongation of life of more than ten years, and it is probable that in cancer of the uterus the results are little less favorable. There is evidence of a clinical statistical character that radiological treatment can compete favorably with treatment by the knife of cancer of the cervix uteri. It has been shown that the proportion of patients who present themselves for treatment only when the disease has advanced beyond the reach of surgical art is very large. How this proportion can be reduced is the great problem. It is obvious that none of the statistical investigations so far carried out, taken by itself, has changed our scale of values; but the cumulative effect of these laborious studies, on the positive side, has increased the precision of our knowledge of the incidence and distribution of cancer, while on the negative side, it has shown the false foundations of many popular theories and superstitions regarding cancer. It is probable that through the gradual improvement in accuracy and completeness of the medical statistics of all nations the way can be best prepared for a really illuminating survey of the cancer problem. At the present time little more can be hoped from the statistical method than an impartial study of strictly defined problems. The time is still far distant when the data of all civilized countries and of all subdivisions of these countries will be strictly comparable in value and significance.

## *FURTHER REPORT ON VACCINATION WITH B C G.*

In an editorial in the August number of the Annals we gave an account of the Lübeck disaster in the vaccination of 246 children in that city with the bacillus-Calmette-Guerin, with the result that up to March 25 there had been 17 deaths from alimentary tuber-

culosis, with 41 living showing evidence of tuberculosis. Later reports show that up to June 3th, 46 children were reported as having died with acute tuberculosis of the alimentary type, and 68 were seriously ill at this time. Much excitement was naturally created by this unfortunate tragic outcome of vaccination against tuberculosis. The affair has received much attention in the press throughout Europe; and has been debated in the Lübeck Parliament. It is reported that criminal proceedings for bodily injury have been started against the medical director of the Lübeck Health Office and the chief physicians of the State and Children's Hospitals. From the Pasteur Institute come strong statements by Calmette as to the harmlessness of his vaccine; and the assertion that the Lübeck accident could only have occurred through an error in the preparation of the vaccine in Germany. Contamination of the BCG culture sent from Paris with virulent human tubercle bacillus in the laboratory in Lübeck has been more than hinted at. Unfortunately following the Lübeck occurrence much publicity has been given in the European press to a situation that has arisen in Ujpest, a town near Budapest. Several hundred children had been vaccinated with the BCG vaccine and of these six have died with clinical tuberculosis, although this is not convincing proof that these deaths can be attributed to the vaccine, yet because of the Lübeck disaster vaccination with BCG has been stopped in this town. If these deaths can be shown to have been a result of the vaccine, the case against the use of the BCG vaccine becomes very serious indeed. Further, wholesale vaccinations with the Calmette-Guerin organism should never have been undertaken as long as there was any doubt anywhere that the BCG strain is a fixed one, and cannot be converted into the human form. Laboratory workers are divided on this extremely important point. Petroff, of Saranac, reported that he had cultivated virulent bacilli from Calmette's BCG vaccine by his isolation of two kinds of colonies "R" and "S", the latter being virulent; and his work has been confirmed in Canada by Read. Watson of the Federal Research Laboratories at Hull has shown that BCG is virulent for calves; and he is convinced that BCG is not a fixed virus. On the other hand, Lange, in a report to the German Health Office maintains that BCG organism is never converted into the human type. He criticizes Petroff's work as wrong, having been based on the study of cultures contaminated with human bacilli: as stated in our previous editorial, Lange regards the Lübeck tragedy as due to the use of a vaccine contaminated with a virulent human strain. How the contamination occurred he is either unable or unwilling to say; but the inference is that the contamination occurred in the laboratory in Lübeck. Surely a Commission should be appointed to settle the question as to the fixed avirulent nature of the BCG vaccine. The question is too important to go begging, or to be allowed to remain in a position of the slightest doubt. If the Calmette claims for the favorable result in thousands of vaccinations already made, without ever a bad re-

sult, can be proved beyond any doubt to be true, then the BCG vaccine is surely a tremendous advance in the fight against tuberculosis; and its value should not be clouded by any suspicion or distrust. On the other hand if the BCG organisms can under any conditions be convertible into virulent tubercle bacilli, human vaccination with them should cease, as being only of the nature of human experimentation, too serious in its possibilities of outcome to be permitted. It is strongly to be hoped that active steps may soon be taken to clear up this ambiguous situation.

# Abstracts

*Studies on the Circulation of the Feet in Diabetes Mellitus with and without Gangrene.* By ISAAC STARR, JR., (Amer. Jour. of the Med. Sc., August, 1930, p. 149.)

In a series of 100 unselected diabetics under treatment the response to the skin of the lower extremities to histamin under standard conditions indicated that 32 percent had a normal circulation in their feet, in 34 percent the circulation was somewhat impaired, in 34 percent markedly impaired. The caloric output of the feet was determined 30 times in 8 diabetics; it was constantly below normal in 6 patients. It is concluded that the majority of diabetics have an abnormal low blood-flow through their feet. The circulation in the feet of certain diabetics may vary markedly with their general condition, but in certain arteriosclerotic diabetics improvement in general condition is not followed by improvement in circulation to the feet. The reaction of the skin of the feet to histamin together with the physical findings permits the demonstration of the presence or absence of adaptations to compensate for sclerotic narrowing of the large arteries, and allows the clinical detection of pathologic change in the minute vessels when the larger arteries are not notably involved. In certain cases the presence or absence of local vasomotor reflex responses can be demonstrated. Such demonstrations permit the assignment of individual cases to one of a number of groups. The great majority of patients with trouble with their feet or history of it fall into two groups characterized by markedly abnormal histamin reactions and generalized arteriosclerotic changes. The data plainly imply that by considering the histamin reaction together with the physical findings a more accurate prognosis can be made than by considering either separately. The types of histamin reaction occurring on the legs of 14 patients with gangerene of the feet are described. The value of this evidence in the selection of treatment and the choice of level of amputation is discussed. An abnormal histamin reaction appears to the author to contraindicate amputation at that level, but a normal reaction is not a guarantee of success. Other factors, the age and strength of the patient, the duration of the disease, the condition of the heart, vessels and blood pressure should be taken into consideration as well as local vascular conditions. The conclusions in this paper are based on reasoning rather than on the data; data on the prognostic significance of the histamin reaction will accumulate but slowly. In the meanwhile it has been found that the response of the skin to histamin together with the physical findings permits an analysis of the conditions of the circulation in the extremities which cannot be obtained by physical examination alone.

*The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City.* By GEORGE G. PACK and ROBERT G. LEFEVRE. (Journal of Cancer Research, June, 1930, p. 167).

During a 12 year period, 19,129 tumors were studied at the Memorial Hospital, 16,565 were malignant. Malignant epithelial tumors composed 89.6 percent of this number; 10.4 percent were sarcomatous. The average age of all the patients was 53.9 years. The average age of the patients with sarcomas was 38.2 years. During the last 75 years there has been no appreciable change in the average ages of occurrence of the more common neoplasms. The decennium 40-50 marks the period when cancer frequency makes its first tremendous increase. Cancers developing in such organs as the breast, thymus, uterus, and prostate,

which undergo physiologic atrophy at definite periods in the life history of the individual have specific relationships to age. The majority of the remaining malignant epithelial tumors are not related to age except that the passing years afford sufficient time for the causative factors to induce degenerations, tissue over-growth, and even cancer. There was evidence to prove that chronologic age is not so important as anatomic and physiologic age as an etiological factor in cancer. The five most common malignant tumors in infants and children were Wilms' adenomyosarcomata of the kidney, ocular glioma, teratoma testis, endothelial myeloma and thymoma. The age incidence of certain cancers increases each year until the normal span of human life is reached. These cancers were melanomas, basal-cell epitheliomas, squamous cell carcinomas of the lip, penis, floor of mouth, buccal mucosa, and inferior alveolus. When percentage corrections are made for the incidence of the various sarcomas on the basis of the proportionate number of persons living during the age periods, it is seen that the incidence of these malignant connective tissue tumors varies only slightly from age 20 to age 80. The benign papillomas of many organs always occur at younger average ages than the carcinomas of the same organ, e.g., the age variance of 22 years for the larynx, 17 years for the vulva, 7 years for the urinary bladder. The tumors which occurred predominantly in females were: mammary adenofibroma, carcinomas of the breast, thyroid, urethra, appendix, and gall bladder. The tumors which occurred predominantly in males were: chondroma, laryngeal papilloma, papilloma of urinary bladder, thymoma, lymphosarcoma, neurogenic sarcoma, bone sarcoma, multiple myeloma, hypernephroma, squamous celled carcinoma of skin; basal-cell epithelioma, carcinomas of the lip, larynx, tonsils, tongue, buccal mucosa, esophagus, stomach, rectum, liver, pancreas, and urinary bladder. There was a constant age difference of 2½ to 4 years for the average ages of male and female patients with the same regional and histological types of cancers; the females were younger than the males. The liability to epidermoid carcinoma of the skin was greatest after the age of a century was passed. Thirty percent of all malignant tumors in patients over 74 years were basal-cell epitheliomas. Brain tumors were uncommon in old people; none occurred in patients over 70 years. Fifty percent of the gliomas were in subjects younger than 25 years. Chrondrosarcoma was the only malignant connective tissue tumor which did not appear in children; the youngest patient was aged 22 years. Giant-cell tumors were the only bone tumors which occurred with greater frequency in females. Contrary to general opinion, bone sarcomas were relatively as frequent at ages 60-64 as at ages 15-19 years. The average age of persons with Ewing's endothelial myeloma was 22 years; the average age of persons with multiple myeloma was 42 years. Carcinoma of the alimentary tract was four times as frequent in men as in women. As far as the ratio of sex was considered, the major liability of the male to cancer of the alimentary tract seemed gradually to approach the female liability from the mouth downward through the digestive tube. Forty-eight percent of the cancers in males were in the alimentary tract and accessory organs. The adenoid cystic epithelioma of muccous membranes is explained by the Durante-Cohnheim embryonic theory of tumor origin. In subjects younger than 25 years carcinoma of the tonsil was 13 times as frequent as carcinoma of the tongue. At the age of 75, carcinoma of the larynx was 32 times as frequent as at age 25. For papillomas of the larynx, the male preponderance was 2 to 1; for carcinomas of the larynx, the male preponderance was 10 to 1. There was evidence to prove the existence of a definite group of carcinomas of the nasal mucosa in children. The average age of patients with carcinomas of the parotid gland was 10 years older than for patients with mixed tumors of the parotid. Carcinoma of the esophagus was very rare in young people; and was quite infrequent in elderly people. Of all cancers of the gastro-intestinal tract, carcinoma of the appendix occurred at the earliest average age, namely 32 years. One out of every 25

patients admitted to the hospital had carcinoma of the rectum. Epidermoid carcinoma of the anus occurred at the youngest average age, of all the regional locations of this histologic type of cancer. Among 100 regional and histologic varieties of cancer, carcinoma of the prostate occurred in patients of the oldest average age, namely 63 years. Yet the incidence for this carcinoma did not increase with advanced age. Teratoma testis is essentially a disease of young men; the incidence declined rapidly after the age of 35. Of all tumors of the female genitalia, vulvar carcinoma occurred in subjects of the oldest average age, namely 60 years. The percentage of vulvar carcinomas occurring in single women was high (16.2 percent). Carcinoma of the cervip uteri was twice as frequent after age 75 as before age 25. The percentage of carcinomas of the body of the uterus in single women was 4 times as great as the percentage of carcinomas of the cervix in single women. The ovary was the only organ in the body wherein the benign and malignant epithelial tumors affected subjects of the same approximate age. The incidence of mammary adenifibromas gradually increased from age 20 to age 50. These fibroadenomas occurred in subjects who averaged 15 years younger than the patients with carcinoma of the breast. One out of every 7 patients admitted to the hospital had mammary cancer. Thyroid adenomas in males have a greater tendency to become carcinomatous than the thyroid adenomas in females. Tumors of the sexual organs occurred at younger average ages in single than in married people, e.g., mammary fibroadenoma and intraductal papilloma, sarcoma of the breast, teratoma testis, carcinomas of the penis, prostate, vagina, cervix, ovary and body of uterus. Cancers of early life, as in breast, stomach, tongue, and rectum, progress more rapidly, disseminate more frequently and recur more often after removal than do their congeners of adult life. Radio-sensitivity is a property found frequently in the malignant neoplasms of youth. Fever is significantly frequent in the case of rapidly growing malignant tumors in young people.

*Malaria Treatment of Paresis.* By WALTER FREEMAN (The American Journal of Syphilis, July, 1930, p. 326).

Freeman concludes from his study that malaria frequently brings about a suppression of the inflammatory manifestations of paresis, and in the successfuly treated cases when death results it is often not from causes connected with the nervous system. Nevertheless, examination of the other organs of the body indicates that the syphilitic infection is still present, and it may show marked activity, particularly in the circulatory system and in the liver. In the small series of cases available for complete study there are indications that syphilitic lesions outside the nervous system are more frequent and sometimes more severe in cases where the malaria had brought about a satisfactory remission in the cerebral inflammation, but this finding may rest upon the relatively greater age of the subjects examined. Extraneural disease in certain of these cases presumably antedated the therapeutic attempt. The malaria is not to be blamed for the occurrence of certain of the late complications such as cirrhosis of the liver. Patients with aortic or myocardial disease often come through the malarial rigors surprisingly satisfactorily, but if the liver is damaged, the outlook is less favorable. Patients subject to convulsive seizures are bad risks, not so much from the malaria itself as from the frequent attending complications. Possibly if due attention is paid to the suppression of these convulsive seizures by control of fluid intake, the results might be better. There are several ways in which the malaria may operate: first, by killing the spirochetes by the high temperature record, second, by stimulation of the reticulo-endothelial system, and third, by the forced drainage of the nervous parenchyma along the perivascular channels into the subarachnoid space. The theory is advanced that the paucity of fibroblastic tissue in the neural parenchyma may prevent the spirochetes from lodging in the brain nests protected from the activities of the fluids and wandering cells, whereas the infection may persist in other organs due to the presence of this tissue. In an undetermined percentage of cases there seems

to be sterilization of the syphilitic infection throughout the body as induced by the return of the serologic reactions to negative. The influence of previous treatment and especially of arsenical treatment cannot yet be evaluated. The figures of certain authors comparing the results of malaria in cases that have received no previous treatment as against those that have received arsenical treatment, cannot be taken at face value unless the time element is properly evaluated, but the figures are suggestive of the possibility of arsenicals preventing the full beneficial action of the malaria. The most outstanding failure of the malaria series was one that had had the most intravenous treatment, and some of the most successful cases had received no treatment before malaria. Antisyphilitic treatment following the exhibition of malaria would seem to be indicated on account of the occurrence of significant lesions outside of the nervous system. The suggestion is made that such treatment should be delayed until some time has elapsed in order to determine by serologic tests whether the activity of the syphilis, serologically speaking, is subsiding sufficiently rapidly. Other pyretogenic agents besides malaria are undoubtedly effective in the treatment of paresis, but there are indications that malaria combines most favorably the three factors suggested above as the means of suppressing the activity of the spirochetes in the central nervous system.

*The Value of Histamine as a Test of Gastric Secretion From a Physiologic Point of View.* By B. P. Babkin. (The Canad. Med. Assoc. Jour., Aug., 1930, p. 268).

Babkin's summary is to the effect that the subcutaneous injection of histamine stimulates the secretion of gastric juice. The acidity of this juice is normal, but its digestive power and content of organic substances is lower than in juice obtained by sham-feeding. The supposition is that histamine activates chiefly the parietal cells of the gastric glands, producing the solution of hydrochloric acid, and in a much lesser degree the peptic and mucoid cells, which supply the juice with enzymes and organic substances. The histamine gastric secretion, therefore, represents largely one particular function of the gastric glands, and does not give a true picture of the total activity of the glands.

# Reviews

*Tropical Medicine.* By Sir Leonard Rogers, C.I.E., M.D., B.S. (Lond.) F.R.C.P., F. R.C.S., F.R.S., Major-General Indian Medical Service, Ret. Medical Adviser to the India Office; Physician and Lecturer, London School of Tropical Medicine; Lecturer on Tropical Medicine, London School of Medicine for Women; Late Professor Pathology, Medical College, Calcutta; and John W. D. McGaw, C. I.E., V.H.S., B.A., M.B., B.Ch., B.A.O., Major-General Indian Medical Service. Formerly Director and Professor of Tropical Medicine, Calcutta School of Tropical Medicine and Hygiene. 536 pages, 77 illustrations. P. Blakiston's Son and Co., Inc., Philadelphia, Penn. Price in cloth $4.00 net.

The writers of this book have had the advantage of many years' experience in clinical, pathological and teaching work in the Tropics. They are convinced that there is a real need for a small work on tropical medicine which will contain only such details of microscopical technique as the general practitioner can carry out in his hospital or practice, and will be devoted chiefly to the recognition and management of the diseases which are commonly met with in tropical and subtropical countries. Most of the works on tropical medicine extant assume that the facilities of up-to-date laboratories are at the disposal of medicine men in the tropics, whereas the truth is that at least 90 percent of the medical men in the tropics have to depend on their own resources and on the simple methods of diagnosis, which are within the reach of the general practitioner. The authors also feel that ther is a need for a small and handy book which will give a broad survey of the field and so serve as an introduction to the subject of tropical medicine. Since in the great majority of medical schools and colleges there are special sourses in pathology, bacteriology, and entomology, much of the material covered by such courses is omitted from this book, as it can be found in the text books on these subjects. This book makes no attempt at completeness; many of the rarer diseases have not been touched on at all, and others have been dismissed in a few lines; and some diseases of considerable importance outside of the limits of the British Empire have received very brief notice. This book is written largely with reference to India; and especial attention has been paid to the geographical distribution of the more important diseases and to maps showing their distribution in that country. The diseases dealt with in this book are classified as far as practicable according to their causal agencies; but in some cases a clinical classification is followed as being more helpful to the student. The authors have retained the more generally known names of common tropical parasites rather than adopt the latest scientific nomenclature, such as "Wucheria" for the more familiar Filaria. The treatment of the material comprises eleven sections: Febrile Diseases Caused by Protozoa; Febrile Diseases Caused by Spirochetes; Febrile Diseases of Uncertain Origin; The Typhus Fever Group; Bacterial Febrile Diseases; Bowel Diseases with Symptoms of Dysentery and Diarrhea; Diseases with the Most Prominent Lesions on the Surface of the Body; Helminthic Diseases; Diseases Caused by Venomous Animals; Diseases Associated with Diet and Diseases Caused by Heat and Light. This book is especially valuable as reflecting the experience of the authors in India; it is, of course written largely from that standpoint; but the general material contained in the volume is of the greatest value to all physicians in tropical and subtropical countries. Especially valuable are the sections on the febrile diseases. No book on tropical medicine has

yet appeared which has such a foundation of practical experience beneath it. The reviewer regrets that the authors did not devote more attention to the pathology of the diseases peculiar to the tropics as that would have added greatly to the value of the work; but they have accomplished excellently what they set out to do in their emphasis of the clinical and practical aspects of tropical diseases. The section on Undulant Fever has not been brought up to date, in the light of American experience, but this again is excusable viewed from the standpoint of their idea of what they wished their book to present.

*Studies on the Diagnosis and Nature of Cancer.* By Various Authors. Being Reprints of Special Articles from the Cancer Review. 240 pages, 22 illustrations. William Wood and Co., New York, 1930. Price in cloth $4.00.

This book consists of reprints of articles, particularly on diagnosis, submitted for the consideration of medical practitioners and students of cancer problem. The British Empire Cancer Campaign is responsible for its publication. It contains the following articles: The Early Diagnosis and Treatment of Cancer of the Bladder by A. Clifford Mason; The Present Position of the Operative Treatment of Breast Cancer by W. Sampson Handley; The Early Diagnosis of Cancer of the Colon by J. P. Lockhart-Mummery; Primary Carcinoma of the Lung with Special Reference to X-ray Diagnosis by P. J. Kerley; The Early Diagnosis of Cancer of the Pharynx and Larynx by St. Clair Thompson; The Metabolism of Tumors by R. K. Cannan; Heredity in Relation to Cancer by E. A. Cockayne; A Review of Recent Statistical Studies of Cancer Problems by M. Greenwood; Malignant Disease of the Thyroid Gland and Its Relations to Goitre in Man and Animals by C. Wegelin; The Metabolism of the Trophoblast by W. Cramer; Bone Sarcoma by A. Kolodny; and Immunity to Transplantable Tumors by W. H. Woglom. These papers are very unequal in interest and value. Mason's article on the early diagnosis and treatment of cancer of the bladder is short, concise, and to the point. Handley's article on the operative treatment for breast cancer is also concise and presents the advantages of the diathermic knife as against cold steel. Cancer of the colon is well summed up by Lockhart-Mummery, but nothnig new is offered. The article on primary carcinoma of the lung is a practical one and covers the ground very thoroughly. Not so much can be said for Wygard's article on the early diagnosis of cancer of the stomach. Of greater practical value is Thompson's article on the early diagnosis of cancer of the throat. Cockgayne's article on heredity in relation to cancer presents a fair, though not overenthusiastic, statement of the case. Of the remaining articles the one by Woglom on immunity to transplantable tumors is the most important, covering as it does the literature of the subject very completely. He concludes that immunity to transplantable tumors is a generalized refractory condition which appears to be entirely unrelated to other forms of immunity. No single organ has yet been proved responsible for its elaboration; nor is it affected by physiological conditions such as age or pregnancy. In its acquired form it is neither hereditary nor passively transferable through the body fluids. It seems probable that natural resistance is only the ability to react so promptly and efficiently that a graft is overcome before it gains a foothold. The outcome of inoculation is determined by an interplay between the hostility of the host and the proliferative vigor of the implant, hence an absolute immunity does not exist. Resistance is effective during the first few days following inoculation but entirely powerless against an established tumor. Nothing may accordingly be hoped for at present in respect to successful therapy from this direction. This volume is of interest to all concerned with the problem of cancer, either from the clinical side, or the pathological, or the experimental.

*The Mycoses of the Spleen.* By Alexander George Gibson, M.D., F.R.C.P., Physician to the Radcliffe Infirmary and Reader in Morbid Anatomy in the University of Oxford. 169 pages, 15 figures.

The Macmillan Company, New York, 1930. Price in cloth, $4.50.

This volume is published in the Anglo-French Library of Medical and Biological Science. In 1913 Gibson put forward the suggestion that certain forms of splenomegaly included in the terms splenic anemia and Banti's disease were the result of an invasion of the spleen by a form of streptothrix, which, he thought, could be demonstrated in the pigmented nodules found in these cases scattered throughout the substance of the spleen. A further study of these has strengthened him in this opinion that they are the cause of the disease, and that a mycelial origin is the only possible explanation of the threads that were described. With these two diseases he now includes acholuric jaundice. The pigmented nodules known as the Gandy-Gamma nodules, from the descriptions by these two workers in 1905 and 1923-4, contain mycelial-like structures staining slate blue with hematoxylin and giving a feeble iron reaction. They do not stain with Weigert's fibrin stain, they are Gram-negative and give no reaction with Van Gieson's stain. Gibson regards these as streptothrix mycelia. In 1925 Nanta and associates found similar bodies in the spleens of cases of splenic anemia which they have interpreted as the mycelia of a fungus belonging to the genus aspergillus. The mycelial nature of the fibers found in the Gandy-Gamna nodule has not been generally accepted. Langeron believes that the supposed mycelia are fibers of fibrin impregnated with iron. Gibson's book is a resumé of his findings and views, with a consideration of those of Nanta, and the criticisms of Langeron. The question of the nature of the Gandy-Gamna nodule and its peculiar inclusions remains unsettled; and the problem can only be settled by the repretition of these observations by numbers of other workers.

*The Chest.* By L. R. Santé, M.D., F.A.C.P., Professor of Radiology and Director of Department, St. Louis University Medical School. Radiologist to the University Group of Hospitals. Annals of Roentgenology. A Series of Monographic Atlases. Edited by James T. Case, M.D., Volume Eleven, 561 pages, 376 roentgen-ray studies and 153 clinical illustrations. Paul B. Hoeber, Inc., New York, 1930. Price $20.00.

The increasing importance of the x-ray examination in the diagnosis of morbid conditions of the chest make a knowledge of the interpretation of films of the chest both desirable and necessary, even imperative. It cannot be expected that the general practitioner will become expert in such interpretation, but he should have sufficient knowledge of this relatively new field of diagnostic aid to understand the general significance of chest films, to be able to follow their expert interpretation with understanding and to acquire a practical acquaintance with the principles of x-ray interpretation. Physical diagnosis has been tremendously enriched by the application of x-ray examinations to the study of diseases of the chest; it is as essential that the physician of today add a practical knowledge of the principles underlying such examinations, as it is for him to acqquire a knowledge of auscultation and percussion. In fact, the writer believes that it is the practitioner who should acquire expert knowledge in the interpretation of x-ray films, in order that he may supplement and check up the knowledge gained by other methods of physical diagnosis. If he depends upon the roentgenologist alone, who usually does not possess a knowledge of other methods of physical diagnosis, there is the danger that he may come to rely too much upon the x-ray film, or even, as is actually the case with some busy practitioners, come to depend upon it alone, to the neglect of the older methods of physical diagnosis. For the practitioner must constantly have in mind the fact that the x-ray film does not tell the whole story of pulmonary disease; there are morbid conditions of the chest not revealed by roentgenological examination. This makes it all the more imperative that the practitioner should at least have a fairly good working knowledge of the interpretation of films. This volume is undertaken for this very purpose, to give a mutual exchange of knowledge for the aid of the clinician. It will also serve as a compilation for the guidance of roentgen-

ologists. The book is divided into three parts: Part I dealing with certain considerations essential preliminary to undertaking chest interpretations; Part II dealing with the evidences of pathology as they appear at roentgenological examination, enumerating all conditions affecting each lung structure and showing as far as possible wherein their roentgenological appearance differs in each case; Part III given over to a detailed consideration of each disease, following it through from inception to termination. In this way, in any roentgenogram of the chest, Part II serves to establish within a few possibilities the identity of a pathological lesion, while Part III completes the differentiation by a detailed account of each possibility established. The material of this book is very complete; the arrangement excellent; and the discussion full and to the point. The illustrations have been beautifully accomplished; each one tells its story clearly and plainly. There is not one single poor one in the book. The volume offers a tremendous aid to the study and diagnosis of chest diseases; and is an essential to the armamentarium of the practicing physician. The book is beautifully gotten up; it is a work of art, reflecting the greatest credit upon the firm of Hoeber. It marks a decided step forward in the study and diagnosis of morbid conditions of the chest.

# College News Notes

## JOHN PHILLIPS MEMORIAL PRIZE

A large number of entries have been made in competition for the 1931 award of the John Phillips Memorial Prize. The submission of dissertations and theses closed on August 31, but it is probable that the Board of Regents of the American College of Physicians will offer the prize of $1500-00 for 1932, as well as for 1931.

Announcement of the winning thesis will be made at least two months in advance of the Baltimore Clinical Session, March 23-27, 1931.

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At the Detroit, 1930, Session of the American Medical Association, Dr. Frank Smithies (Master), Chicago, was elected by the House of Delegates, a member of the Council of Scientific Assembly to serve for a period of five years.

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Dr. Meldrum K. Wylder (Fellow), Albuquerque, N. M., read a paper on "The Preventive Measures in Pediatrics" before the last meeting of the New Mexico State Medical Association.

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At the Detroit Session of the American Medical Association, the following Fellows from Georgia participated in the program:

Dr. W. R. Houston, Augusta, as Vice Chairman of the Section on the Practice of Medicine;

Dr. James E. Paullin, Atlanta, as a member of the Executive Committee of the Section on the Practice of Medicine;

Dr. Stewart R. Roberts, Atlanta, read a paper on "Agranulocytic Angina" before the Section on the Practice of Medicine;

Dr. E. C. Thrash, Atlanta, a delegate from Georgia, served as Chairman of the Reference Committee on Amendments to the Constitution and By-Laws of the House of Delegates;

Dr. Allen H. Bruce, Atlanta, as a member of the Board of Trustees.

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At the last session of the American Medical Association held at Detroit, Mich., Dr. Samuel Weiss read a paper on and demonstrated a new gastroscope. He also had a booth in the scientific exhibit where models and charts for teaching gastroenterology were shown. The main feature was a phantom stomach with numerous cuts fitting into it showing normal and pathological conditions of the gastric mucosa. This model is the only one in existence at the present time, and was favorably commented upon by those who viewed it.

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Dr. Edgar Erskine Hume (Fellow), M. C., U.S.A., received the honorary degree of Doctor of Laws from the University of Kentucky on June 2, 1930.

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Dr. Warren Pearce (Fellow) with Dr. R. A. Harris, Quincy, Ill., is the author of an article entitled "Lead Poisoning: With An Analysis of Employees of an Enameling Plant" in the July Issue of the Quincy Medical Bulletin.

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Dr. Alfred Meyer (Fellow), New York, N. Y., has been engaged in research work at Woods Hole, Mass., during the summer months. Each year, teachers in all branches—biology, physics, zoology, physiology, botany, medicine, anthropology, chemistry and subdivisions—assemble there for all sorts of study and research in their respective lines. Excavations have been begun for an oceanographic institute to be run by a separate Board of Trustees from the Maine Biological Laboratory.

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Dr. G. Harlan Wells (Fellow), Philadelphia, Physician-in-Chief to the Hahne-

mann Hospital, is the author of an article, "Digitalis: Relative Efficiency and Stability of the Various Preparations of Digitalis", which apeared in the July Number of the Hahnemannian Monthly.

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Dr. William W. Cadbury (Fellow), Canton, China, was elected Superintendent of the Canton Hospital during June. This hospital has now been transferred to Lingnan University, and is the first hospital to be established in China along western lines. It has been engaged in active service for nearly ninety years.

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Dr. Crawford R. Green (Fellow), Troy, N. Y., is author of the contributed article for July in the Hahnemannian Monthly, "Leaves from a Therapeutic Note-book". The original paper was read on April 22, 1930, before the Homeopathic Medical Society of the State of New York, at Brooklyn.

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Dr. Clarence R. Bell (Fellow) of the Medical Corps of the U. S. Army, is now on duty at the Sternberg General Hospital, Manila, P. I., as Chief of the Medical Service, where he relieved Dr. Luther R. Poust (Fellow), Major, M.C., U.S.A., who has been transferred to another station.

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Dr. Wililams S. McCann (Fellow) and Dr. John R. Williams (Fellow), Rochester, N. Y., were recently appointed examiners in medicine by the National Board of Medical Examiners.

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Dr. J. A. Myers (Fellow), Minneapolis, is the author of a new book entitled "Tuberculosis Among Children", published by Charles C. Thomas, Springfield, Ill.

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Dr. Frederick J. Farnell (Fellow), Providence, R. I., is the author of a series of articles on modern aspects of social work covering "The Feeble-Minded", "The Mentally Diseased", "The Delinquent and the Criminal", with a special introduction and conclusion in the Evening Bulletin of Providence during July.

Dr. Carl V. Vischer (Fellow), Philadelphia, Assistant Physician to the Hahnemann Hospital, held a special Medical Clinic on "Pulmonary Tuberculosis" at the hospital on May 1. There were lantern slide ilustrations, and the entire clinic was published in the July Issue of the Hahnemannian Monthly.

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Dr. August S. Ketch (Fellow), Altoona, Pa., was the author of an article entitled "Electrocardiogram of Dextrocardia" in the July Issue of the Pennsylvania Medical Journal.

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Dr. Jesse L. Lenker (Fellow), Harrisburg, Pa., after touring France and Germany during the summer, attended the International Hygiene Exhibit and World Health Conference in Dresden, Germany.

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Dr. Arthur W. White (Fellow), Oklahoma City, Okla., contributed an article entitled "Amebiasis—Present Day Interest" to the July Issue of the Journal of the Oklahoma State Medical Association.

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Dr. Everett S. Lain (Fellow), Oklahoma City, Okla., has visited various European centers during the summer, and attended the International Dermatological Association's meeting at Oslo, Norway.

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Dr. Henry M. Moses (Fellow), Brooklyn, and Dr. Joseph G. Terrence (Associate), Brooklyn, returned about August 1 from the Tour of the Thermal Resorts of France at the invitation of the French Government. At the close of the official tour, they visited hospitals and physicians on tour through Switzerland, Italy, Austria, Germany and England.

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Dr. Ray M. Balyeat (Fellow), Oklahoma City, with Dr. Fannie L. Brittain, is author of an article on "Allergic Migraine: Based on the Study of Fifty-five Cases" in the August Issue of the American Journal of the Medical Sciences. In the same issue, Dr. I. I. Lemann (Fellow), New Orleans, is author of the article on "The Futility of Alkali Treatment in Diabetic Coma. Analysis of Forty-seven Cases."

In the August Issue of the Southern Medical Journal, the following articles by Fellows of the College appeared:

Dr. Sinclair Luton (Fellow), St. Louis,
"Comparison of Methods Used for Estimating the Size of the Heart."

Dr. C. S. Holbrook (Fellow), New Orleans,
"Encephalitis and Encephalomyelitis Following Vaccination Against Smallpox: Report of Five Cases."

Dr. Oliver C. Melson (Fellow), Little Rock,
"Limits of Normal From a Clinician's Point of View."

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Dr. Claude L. Holland (Fellow), Fairmont, W. Va., pursued postgraduate study in Pediatrics at the Harvard Medical School during the summer.

Dr. Alfred Gordon (Fellow), Philadelphia, is the author of "The Problem of Neoarsphenamine-Resistance and Neoarsphenamine-Intolerance (Hypersensitivity) in Neurosyphilis" in the July Issue of the Journal of Chemotherapy.

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In the August Issue of Radiology, the following Fellows contributed the articles indicated:

Dr. Preston M. Hickey, Ann Arbor, Mich..,
"Economic Problems of the X-Ray Laboratory."

Dr. Arthur C. Christie, Washington, D. C.,
"The Work of the Committee on the Cost of Medical Care."

Dr. Harold Swanberg, Quincy, Ill.,
"The Pre-Radium Treatment of Carcinoma of the Uterine Cervix."

Dr. Alden Williams, Grand Rapids, Mich.,
"New Experiments on Cancer Cure."

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Dr. Preston M. Hickey (Fellow), Ann Arbor, Mich., was the recipient of the degree of Doctor of Science at the June graduation of the Detroit College of Medicine and Surgery.

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Dr. Edwin W. Gehring (Fellow), Portland, Maine, presented a paper on John Hunter entitled "A Great Scotsman and His Brother" at the Aroostook (Maine) County Medical Society, recently.

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Dr. Eugene H. Drake (Fellow), Portland, Maine, conducted a clinical conference on the heart, and Dr. Elton R. Blaisdell (Fellow), Portland, Maine, conducted a similar conference on diabetes and nephritis at the Maine General Hospital, June 2.

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Dr. Thurman D. Kitchin (Fellow), Wake Forest, N. C., who has been Dean of the Medical School at Wake Forest for thirteen years and who is a past President of the Medical Society of the State of North Carolina, has been elected President of Wake Forest College.

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Dr. John B. Youmans (Fellow) has been appointed Associate Professor of Medicine and also Director of graduate instruction on the medical faculty of Vanderbilt University, Nashville, Tenn.

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Dr. Hubert Work (Fellow), Denver, Colo., spoke on the subject, "The Doctor in Politics," at the annual meeting of the Colorado State Medical Society at Peublo, September 9-11.

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Dr. Constantine F. Kemper (Fellow), Denver, Colo., addressed the San Luis Valley Medical Society at Monte Vista (Colo.), June 21.

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Dr. James H. Hutton (Associate), as President of the Chicago Medical Society, has named a Committee to aid in the survey of Illinois hospitals for the mentally diseased. Among those named on the Committee are Dr. Roibert S. Berghoff (Fellow) and Dr. George W. Hall (Fellow), both of Chicago.

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Dr. Philip S. Hench (Fellow), Rochester, Minn., addressed the Jefferson County (Ohio) Medical Society during the summer on "Rheumatic Diseases and Gout—Their Differential Diagnosis and Treatment."

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Dr. Archibald H. Beard (Fellow), Minneapolis, Minn., addressed the Barron-Polk-Washburn-Sawyer-Burntt County Medical

Society at its June meeting on "Diabetes Mellitus and Vascular Disease."

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Dr. Ray C. Blankinship (Fellow), Madison, Wis., addressed the Marinette-Florence County (Wisconsin) Medical Society, recently, on "Medical Management of Peptic Ulcers."

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Dr. Laurence R. DeBuys (Fellow), New Orleans, was elected President-Elect of the American Pediatric Society on June 17.

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Dr. David Riesman (Fellow), Philadelphia, addressed the Sixth Clinical Congress of the Connecticut State Medical Society at New Haven, September 16-19, on "Blood Pressure."

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Dr. William E. Gardner (Fellow), Louisville, Ky., delivered a paper on "Some Inflammatory and Degenerative Conditions of the Central Nervous System Due to Specific Infection" before the Third District (Kentucky) Medical Society's meeting, July 9.

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Dr. Warfield T. Longcope (Fellow), Baltimore, Md., was a guest speaker at the annual meeting of the Minnesota State Medical Association at Duluth, July 14-16.

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Dr. Louis Faugeres Bishop (Fellow), New York, N. Y., addressed the Lake Keuka Medical and Surgical Association, comprised of twenty-two counties of western and central New York, at Lake Keuka, July 10-11, on "Analysis of One Hundred Cases of Cardiac Pain, as Seen in Office Practice."

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Dr. Charles F. Martin (Master), Montreal, Que., will address the third annual graduate fortnight of the New York Academy of Medicine, October 20-21, on "Continued Education of the Practitioner."

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Dr. Ernest E. Irons (Fellow), Chicago, Ill., will also deliver a paper on "Facts and Fancies Concerning Vaccines and Nonspecific Therapy."

Dr. John P. Munroe (Fellow) and Dr. Archibald A. Barron (Fellow), with Dr. William Allan, all of Charlotte, N. C., discussed the subject of pellagra at the summer meeting of the York County Medical Society.

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Dr. Henry Boswell (Fellow), Sanatorium, Miss., was one of the scheduled speakers at the state conference on tuberculosis, held at Salisbury, N. C., August 7, of the North Carolina Tuberculosis Association.

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Dr. Thomas Klein (Fellow), Philadelphia, Pa., has been appointed Professor of Applied Therapeutics on the faculty of the Temple University School of Medicine.

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Dr. Waller S. Leathers (Fellow), Nashville, Tenn., has been elected President of the National Board of Medical Examiners.

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Dr. J. Gurney Aaylor (Fellow), Milwaukee, was elected a member of the National Board of Medical Examiners, representing the Wisconsin State Board of Medical Examiners.

Dr. Charles A. Elliott (Fellow), Chicago, Dr. William DeB. MacNider (Fellow), (Chapel Hill, N. C., and Dr. Walter W. Palmer (Fellow), New York City, were elected members of the Board at large. The Constitution has been amended so as to increase the membership from twenty-one to twenty-seven. This was necessitated by a ten per cent increase in the number taking examinations during the present year as compared with the previous year. Forty states, in addition to the territories of Hawaii, Porto Rico and the Canal Zone, now recognize the national certificate. England, Scotland, Ireland and Spain give partial recognition to the Board's examinations.

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Dr. Adolph Sachs (Fellow) with Dr. Raymond L. Traynor, of Omaha, Nebr., is author of an article entitled "Ulcerative Colitis—With Special Reference to Diet" in the August Issue of the Nebraska State Medical Journal.

Dr. Floyd Clarke (Fellow), Omaha, is author of an article entitled "Acrodynia

With Report of Three Cases" in the same issue of the above journal.

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Acknowledgment is made of the receipt of the following reprints of publications by members of the College, which have been indexed and added to the College Library:

Dr. Samuel Ayres, Jr. (Fellow), Los Angeles, Calif.:

"Gastric Secretion in Psoriasis, Eczema and Dermatitis Herpetiformis"

"Pityriasis Folliculorum (Demodex)"

"Eczema—Some Recent Contributions to its Study"

Dr. Miles J. Breuer (Fellow), Lincoln, Nebr.:

"The Treatment of the 'Early' Case of Tuberculosis"

"Tuberculosis: The Nature of the Diagnostic Problem"

Dr. Carl R. Howson (Fellow), Los Angles, Calif.:

"Climate In Pulmonary Tuberculosis"

"Heliotherapy in Pulmonary Tuberculosis—Its Possibilities and Dangers"

"Explaining Artificial Pneumothorax to the Patient"

"Standardization in Artificial Pneumothorax"

Dr. E. A. Sharp (Fellow), Detroit, Mich.:

"An Antianemic Factor in Desiccated Stomach"

"Acute Influenzal Infection—An Interpretation of Mild Respiratory Diseases"

Dr. George L. Waldbott (Associate), Detroit, Mich.:

"Hypertension Associated with Allergy"

*OBITUARY*

Dr. Robert Hall Babcock (Fellow), Chicago, Ill., died, June 28, at Green Lake, Wis., of heart disease; aged 79.

Dr. Babcock was born at Watertown, New York, received his A.B. and A.M. degree from Western Reserve University, his medical degree from the Chicago Medical College, 1878, and also from the Medical Department of Columbia College, New York City, in 1879. He was awarded the honorary degree of LL.D. from the University of Michigan in 1910. His practice had been devoted to Internal Medicine since 1883. From 1891 to 1905, he was Professor of Clinical Medicine and Diseases of the Chest at the College of Physicians and Surgeons, Chicago, and Attending Physician to Cook County Hospital. He was Professor of Clinical Medicine and Physical Diagnosis at the Chicago Postgraduate Medical School from 189 to 1896. In later years, he was Consulting Physician to the Passavant Hospital and a member of the associate staff of the St. Luke's Hospital.

Dr. Babcock was President of the Chicago Tuberculosis Institute from 1916 to 1921; President of the American Medical Association, 1901; President of the Mississippi Valley Medical Association, 1911; a Fellow of the American College of Physicians since 1916. He was a member of the American Congress of Physicians and Surgeons, the National Tuberculosis Association, Institute of Medicine of Chicago, Chicago Society of Internal Medicine, American Climatological and Clinical Association, National Association for Study and Prevention of Tuberculosis, Tri-State Medical Society, emeritus member of the Association of American Physicians, honorary member of the Edinburgh Medico-Chirurgical Society, member of the University Club, Chicago, Delta Kappa Epsilon Fraternity and the Delta Kappa Epsilon Club of New York City. He was the author of several books, among them "Diseases of the Heart and Arterial System," "Diseases of the Lungs" and "Your Heart and How to Take Care of it."

Dr. Babcock was among the earliest members of the College, was a regular attendant at its Annual Clinical Sessions and exerted a wholesome influence on the development of its ideals and purposes.

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Dr. Nicholas Lukin (Associate), New York, N. Y., died June 10, 1930, aged 60 years. Dr. Lukin graduated from the University and Bellevue Medical College in 1908. He was Chief of the Clinic, and Adjunct, Department of Internal Medicine, of the Bronx Hospital, and Cardiologist to the Bronx Maternity Hospital.